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GASTROESOPHAGEAL REFLUX DISEASE: THE DIAGNOSTIC VALUE OF MANOMETRY, AND THE EFFECTS OF FUNDOPLICATION ON ESOPHAGEAL MOTOR FUNCTION

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1984.	DR. K. L. BOWES.

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GASTROESOPHAGEAL REFLUX DISEASE: THE DIAGNOSTIC VALUE OF MANOMETRY, AND THE EFFECTS OF FUNDOPLICATION ON ESOPHAGEAL MOTOR FUNCTION

by

(C) PAUL DENIS MURPHY

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

IN

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.....
Supervisor

.....

.....

Date: ..Dec 19/83.....

DEDICATION

To the memory of

John Heffernan O'Reilly, F.R.C.S.,

late County Surgeon,

Waterford, Ireland.

A B S T R A C T

This study was undertaken to investigate three areas of controversy in gastro-esophageal (GE) reflux disease:

1. The place of manometric measurements of sphincter function in diagnosis of the condition had not been established.

2. Indirect evidence had indicated that a defect in esophageal motor function might play a role in pathogenesis of the disease, but direct (manometric) evidence was lacking.

3. The effects of fundoplication on the lower esophageal sphincter were the subject of controversy, and its effects on the body of the esophagus had not been determined.

— oOo —

The study was in two parts.

STUDY A: Assessment of Three Manometric Measurements of Lower Esophageal Sphincter (LES) Function, followed by an Acid-infusion Test (AIT)

The subjects were 41 healthy volunteers (controls) and 68 patients who had symptomatic GE reflux of varied severity clinically and endoscopically. The patients were rated grade I, II, or III, according to the severity of symptoms, then subjected to endoscopy and divided into three grades according to the findings.

Manometric measurements were made of LES pressure in resting state (R.LESP) and in response to sustained abdominal compression (C.LESP), and distal esophageal pressure in response to sudden compression of the abdomen (common-cavity test, CCT), followed by AIT. All of the test values were assessed independently and without knowledge of

subject/patient status, being rated individually as marked positive(++), positive(+), equivocal, or negative indicators of GE reflux disease. Diagnostic value of the tests individually and in combination, was assessed. Finally, the probability of a randomly selected person with a given number of positive test responses was calculated for a range of incidence values of G.E. reflux disease.

STUDY B: Assessment of R.LESP, C.LESP, LES response to Deglutition, and Esophageal Peristalsis, in Control Subjects and Pre- and Post-fundoplication in Patients with Symptomatic GE Reflux

The subjects were 18 volunteers (controls) and 32 patients with symptomatic GE reflux disease. The latter were studied prospectively (pre-operatively) and 6 months after fundoplication.

R.LESP and C.LESP were measured, together with the amplitude and duration of LES relaxation in response to deglutition and of LES contraction after deglutition, and any residual LES pressure on relaxation.

Esophageal contraction in response to 10 solicited wet swallows (5-ml bolus of H_2O): Recordings were made of contractions in the upper, middle, and lower esophageal regions, and the results were expressed as the mean of the 10 measurements at each site. Also, the incidence of aperistaltic contractions was recorded.

RESULTS AND CONCLUSIONS

Positive R.LESP and C.LESP responses were highly specific for GE reflux disease (98% and 96% respectively).

In the patients, mean R.LESP was significantly reduced ($p<0.001$) but equivocal or negative results were obtained in 32%. C.LESP was significantly decreased in all patients ($p<0.001$), and C.LESP values had

greater diagnostic sensitivity (81%) than R.LESP (68%). CCT was a useful adjunct to routine manometry (78%) sensitive, 83% specific), as was AIT + in <5 min (78% sensitive, 91% specific). An R.LESP or CCT ++ response was 100% specific but of poor sensitivity (31% and 59% respectively). In combination, two or more positive test responses were 93% sensitive and 95% specific for GE reflux disease. At a 15% incidence level, two or more positive tests indicated a 78% probability of the disease, and three or more + results a 99% probability.

Manometric measurements correlated with endoscopic grading but not with the severity of symptoms.

Aperistaltic esophageal contractions were seen pre-operatively in 38% of the patients but in none of the controls. In the patients, both amplitude and duration of peristaltic esophageal contractions were significantly lower pre-operatively ($p<0.001$) than in the controls.

Post-fundoplication, R.LESP returned to normal levels; however, C.LESP was normal in only 38%, indicating that an abnormal adaptive LES response to abdominal compression had not been corrected. Sphincter relaxation in response to deglutition was impaired, suggesting that the part played by fundoplication in preventing GE reflux is mechanical rather than physiological. Peristaltic amplitudes returned to normal postoperatively, indicating a secondary rather than a primary motor abnormality in GE reflux disease. The incidence of aperistaltic contractions increased after the surgery (to 56%), suggesting that fundoplication itself may induce an esophageal motor abnormality.

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INTRODUCTION

Gastroesophageal (GE) reflux disease is a common disorder which until recently has been poorly understood[1]. With improved manometric techniques[2], and since the identification of the lower esophageal sphincter by Fyke, Code and Schlegel in 1956[3], much has been learned of the pathophysiology of the condition[4]. Untreated, GE reflux disease may have serious sequelae. The first satisfactory anti-reflux procedure was developed by Nissen in the 1950's[5]. Many patients present with atypical symptoms[6], and some patients presenting with complicated GE reflux disease have experienced only minor symptoms. Thus, the accurate diagnosis of this condition assumes great importance in these instances. Unfortunately, no single test has been accepted as the standard for diagnosis of GE reflux, leaving the clinician in a quandry when presented with a difficult case[7].

Resting lower esophageal sphincter pressures are frequently normal in reflux patients, and the functions of the esophagus and stomach may play a role in the pathogenesis of the disease[8].

ANATOMY

Body of the esophagus

The esophagus is a musculomembranous tube which acts as a conduit for ingested food between the pharynx and the stomach. At rest, it is

closed at its upper and lower ends by the upper and lower esophageal sphincter mechanisms. In the adult, it is 20 to 22 cm long, and the gastroesophageal junction lies 40 cm distal to the incisor teeth[9].

Relations

The esophagus commences at the lower border of the cricopharyngeus muscle(C6). In its course it traverses cervical, thoracic, and abdominal regions. In its cervical part, it extends to the level of the suprasternal notch (T2-T3) and runs between the trachea and the spinal column. The recurrent laryngeal nerves run bilaterally in the grooves between the trachea and the esophagus. The carotid sheaths run anterolaterally on either side of the esophagus. The lateral aspect of the lobes of the thyroid and the parathyroid glands rest on the esophagus.

As it descends into the chest the esophagus remains in intimate relationship with the posterior wall of the trachea. Further down, the esophagus is crossed by the aortic arch, which indents it on its left side. At its mid-thoracic level, the esophagus is bounded on its right by pleura, and on its left by descending aorta and pleura. Anterior to it lie the left main bronchus, and, lower down, the pericardium. Posteriorly, the esophagus lies on the vertebral column and its associated muscles, with the intercostal arteries and veins interposed. The azygos vein runs posteriorly to the esophagus. The thoracic duct runs to the right of the esophagus in the lower mediastinum and crosses to the left in the upper mediastinum.

In the lower thorax, the esophagus curves anteriorly and slightly to the left of the aorta, to enter the esophageal hiatus of the diaphragm at the level of T10.

The abdominal portion of the esophagus is short, being at most 2 to 3 cm long. Anteriorly and to the right lies the posterior aspect of the left lobe of the liver. Posteriorly, it rests on the crura of the diaphragm, and to the left may come into close contact with the spleen.

The esophageal lumen is narrowed where it is crossed by the aortic arch, the left main bronchus, and in the area of the lower esophageal sphincter mechanism, at or slightly above the diaphragmatic hiatus.

Structure - Macroscopic

The esophagus has no serosal layer, and consists of outer and inner muscular layers, submucosa, muscularis mucosa, and mucosa.

The outer muscle layer fibers run in a longitudinal direction, with the inner muscle layer fibers running in a circular direction. There is no distinct boundary between these two layers, as fibers from the two layers cross over to a limited extent. In the proximal 2 to 6 cm of the esophagus, the muscle layers consist entirely of striated muscle. From there on, smooth muscle fibers gradually become more abundant, so that at a distance of 4 to 8 cm from the superior end, smooth muscle fibers constitute 50% of the musculature. The distal esophagus consists entirely of smooth muscle.

The submucosal layer is a well developed layer of loose areolar tissue, containing blood vessels, lymphatics, and nerves. The

muscularis mucosa is a single layer of longitudinally orientated smooth muscle fibers.

The mucosa of the esophagus consists of stratified non-keratinizing squamous epithelium, except for the distal 1 cm, where a sharp transition to simple columnar epithelium occurs - the Z line.

In cross-section, the lumen of the empty esophagus has a collapsed stellate appearance, brought about by 7 to 10 longitudinal folds in the mucous membrane, which disappear during the passage of a food bolus owing to dilatation, only to reappear at the same site afterwards[9].

Structure - microscopic

In microscopic section, the esophagus contains the four layers which characterize the tubular digestive system: the mucous membrane, the submucosa, the muscular layers, and the adventitia.

The mucous membrane of the esophagus is composed of an epithelial membrane, which is supported by a thin layer of connective tissue, (the lamina propria) and a thin layer of smooth muscle (the muscularis mucosa). The epithelium is of the stratified squamous type, with a basal or germinative layer made up of cylindrical, basophilic cells. This basal layer is covered by several intermediate layers of polyhedral cells, which, although becoming progressively flatter, retain their nucleus. The flatter surface cells desquamate as single cells or in small groups. Keratinization does not occur. The basal cell layer sends intermittent dermal papillae towards the esophageal lumen, the papillae being covered in seven or eight layers of polyhedral cells. The basal

cell layer rests on a distinct and moderately dense basal lamina, visible on electron microscopy.

The lamina propria is composed of loose areolar connective tissue, containing collagen and elastic fibres but very few cells. The mucularis mucosa comprises a thin layer of longitudinal smooth muscle fibers, and forms a boundary between the lamina propria and the submucosa.

The submucosa is a thick layer of dense fibro-connective tissue, containing a rich elastic meshwork and large blood vessels. Esophageal glands are found in this layer, and their ducts penetrate the muscularis mucosa to open between the epithelial ridges of the mucosa.

The muscular layer comprises an inner circular and outer longitudinal layer, which, as has been noted, consists of striated fibers in the proximal and smooth muscle fibers in the distal esophagus. However, this representation is a simplification of a structure that is actually much more complex[10]. The longitudinal muscle fibers do not directly follow the long axis of the esophagus, but behave as an elongated spiral, turning around one quarter of the esophageal circumference. The inner circular muscle layer is thicker than the outer longitudinal layer. The circular muscle fibers only run horizontally in the isolated and retracted esophagus. In situ, their course is that of an elliptical spiral that winds its way down the esophagus.

The "longitudinal" and "circular" layers are really representations of a polar "screw" system. With this screw arrangement, the muscle

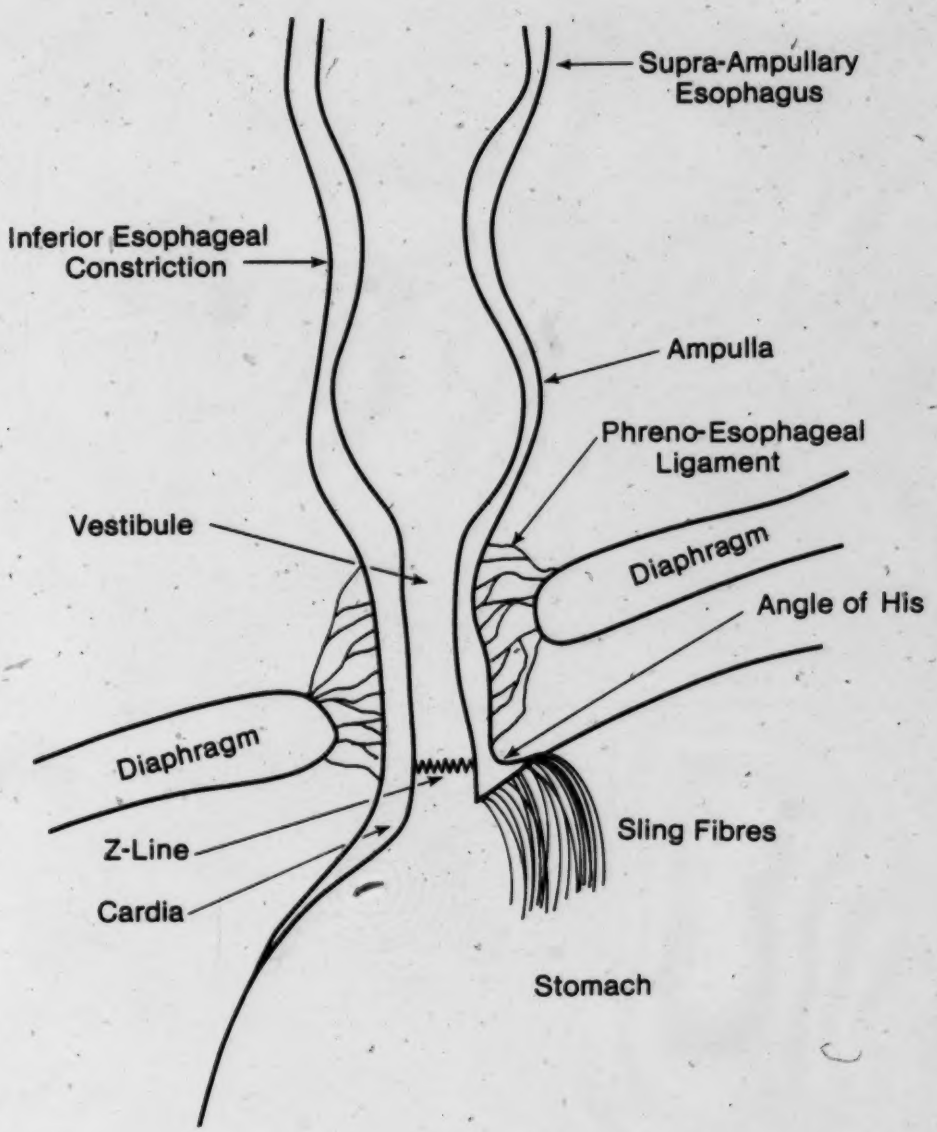
bundles may be represented as being arranged around a cone: the distance from the lumen is ever decreasing, while the beginning and end of the bundle are located at different vertical levels. The screw may be ascending or descending, and may run clockwise or anticlockwise. The outer fibers of the screw turn quite steeply, becoming more horizontal as they approach the lumen. Thus, the transition from "longitudinal" to "circular" layers is unevenly distributed around the esophageal circumference.

The esophagogastric junction (Fig. 1)

The term "cardia" has long been used to describe the esophageal orifice of the stomach. The term was first used by Galen in the 2nd century B.C.[11], as he noticed the similarity between symptoms arising from the upper end of the stomach and those produced by heart disease. Many conflicting anatomical terms have been used to describe the lower esophageal segment and esophagogastric junction, and they may be summarized as follows: the distal esophagus, just above the diaphragm, exhibits a dilated segment (vormagen, esophageal ampulla, phrenic ampulla), above which level is the supra-ampullary esophagus. Below the ampulla is a narrowed segment which runs through the diaphragmatic hiatus (vestibule, cardiac antrum, physiologically empty segment), and which is surrounded by the phreno-esophageal ligament[11]. In this segment, and usually 1 cm proximal to the stomach, in the intra-abdominal segment of the esophagus, lies the transition zone (Z-line) between squamous and columnar epithelium. The esophagus now joins the

FIGURE 1

Schematic representation of the esophagogastric junction


Supra-Ampullary Esophagus
Inferior Esophageal Constriction
Ampulla
Phreno-Esophageal Ligament
Vestibule
Diaphragm
Angle of His
Diaphragm
Sling Fibres
Z-Line
Cardia
Stomach

stomach proper at the cardia, and forms an acute angle (angle of His, Incisura Cardiaca) at its point of entry. The muscle layers of the esophagus become continuous with those of the stomach. The longitudinal muscle layer diverges distally from the cardia and becomes the outer longitudinal muscle layer of the stomach. The inner circular muscle layer of the esophagus continues into the middle muscle layer of the stomach, whose fibers run horizontally, and into the inner muscle layer, whose fibers turn in a sling-like manner across the cardia. Intraluminally, the gastric mucosa is gathered in coarse folds (mucosal rosettes) about the cardiac orifice[12].

The phreno-esophageal "ligament" or membrane is a fibroelastic structure arising mainly from the subdiaphragmatic fascia, and divides into ascending and descending leaves to circumferentially surround the vestibular complex[13]. From the attachment to the esophagus, fibroelastic fascicles extend inwards to join intramuscular and submucosal fibrous tissue over a distance of 2 to 5 cm above the squamo-columnar junction.

The esophageal hiatus of the diaphragm is a muscular tunnel 2 to 3 cm long and, with some individual variations, composed mainly of the right diaphragmatic crus[11]. The crura of the diaphragm arise by tendinous sheets from the anterolateral aspect of the first four lumbar vertebrae and their intervertebral disks, being separated from each other by the celiac trunk. The crura are inserted into the central tendon of the diaphragm. As it ascends ventrally, the right crus divides into right and left portions, forming the right and left margins

of the esophageal hiatus.

There has been much argument about the precise definition of the esophagogastric junction[14]. Among the definitions proposed are the squamo-columnar junction, the angle of His, the peritoneal reflection of the stomach, and the junction of the inner circular muscle layer of the esophagus with the inner oblique or sling fibers of the stomach. The squamo-columnar junction, although it can be visualized at endoscopy and its site confirmed by biopsy, and usually lies 1 cm above the cardia, shows considerable variation between individuals. The angle of His, or point at which the tubular esophagus joins the stomach, is readily identifiable in normal individuals; however, it becomes ill-defined in patients with a widened hiatus or hiatal hernia. The peritoneal reflection shows considerable variation and does not correspond on the anterior and posterior aspects of the gastroesophageal junction. Anatomically, the junction of the esophageal circular muscle layer with the gastric sling fibers is the most acceptable definition of the gastroesophageal junction. The mucosal junction usually occurs at this point, and esophageal submucosal glands are only found above this level. From a practical point of view, the squamo-columnar junction or Z-line provides the best clinical definition of the gastroesophageal junction; this, however, must be qualified by the statement that if the Z-line clearly lies more than 2 cm above the opening of the esophagus into the stomach, or above a level where esophageal submucosal glands are found, then the term "esophagus lined with columnar epithelium" must be employed[15].

Arterial blood supply; venous and lymphatic drainage

The arterial blood supply of the esophagus is via branches of the inferior thyroid artery in its cervical portion; via branches of the bronchial arteries, right intercostal arteries, and at least two direct aortic branches in its thoracic portion; and via branches of the left gastric and left lower phrenic arteries in its abdominal portion, with occasional branches from the aorta, the splenic artery, and the celiac trunk.

The esophageal veins may be classified as intrinsic and extrinsic veins. The intrinsic venous system consists of a subepithelial plexus which runs in the lamina propria, which communicates with the subglandular venous plexus of the stomach; and a submucosal venous plexus which consists of 10 to 15 longitudinal veins, evenly distributed around the circumference of the esophagus and which join the submucosal veins of the stomach distally.

Perforating veins arise from the longitudinal submucosal plexus and perforate the muscle layers at frequent intervals, and unite on the outer surface of the esophagus to form the extrinsic periesophageal veins, which drain into the azygos, hemiazgygos, and intercostal venous systems. In the abdomen, the extrinsic periesophageal veins communicate with the left gastric and inferior phrenic veins.

The lymph vessels in the most proximal part of the esophagus drain into the deep cervical chain of lymph nodes; all the others drain into the nearest available group of lymph nodes. In the upper two thirds of the esophagus, lymph flow is mostly directed cranially, in the lower third, mostly distally(9).

Nerve Supply

Parasympathetic innervation

The vagal nerves provide the parasympathetic nerve supply to the esophagus, with afferent and efferent cell bodies in the nucleus dorsalis and the nucleus ambiguus. The cervical esophagus is innervated by the recurrent laryngeal branches of the vagal nerves. In the thorax, the vagal nerves join with fibers from the sympathetic chain to form the esophageal plexus. Extensive cross connections occur between both vagi, and from this plexus is formed the anterior and posterior vagal trunks that enter the abdomen.

Sympathetic innervation

Cell bodies in the 4th to 9th thoracic spinal segments send preganglionic fibers to the sympathetic chain, the greater splanchic nerve, and the celiac plexus. Postganglionic fibers either reach the esophagus directly, or via the vagal nerves.

The parasympathetic and sympathetic nerves form a series of plexuses in the adventitial, muscular, and submucosal layers of the esophagus. The adventitial plexus has been mentioned above. Preganglionic parasympathetic vagal fibers penetrate the muscle layer and terminate on the ganglia of the myenteric plexus of Auerbach, which lies between the longitudinal and circular muscle layers. Thin postganglionic fibers from the myenteric plexus synapse with muscle fibers. Branches of both the myenteric and adventitial plexuses form

the network of the submucosal plexus of Meissner. A thin web of fibers occupies the lamina propria, and some delicate fibers from it terminate between the basal cells of the squamous epithelium.

Afferent innervation

Sensation from the upper esophagus is carried by parasympathetic fibers, while sensation from the lower esophagus travels with sympathetic fibers. Otherwise, the distribution of afferent nerves or their mode of transmission is unknown. Mechanoreceptors have been demonstrated in the wall of the cat esophagus[16]; there is only indirect evidence that other sensory receptors such as osmoreceptors and free nerve endings may be present in the esophagus[17,18].

Embryology

Developmentally, the esophagus and trachea commence as a single tube. Septation of this tube occurs, and separation of the esophagus and trachea is complete by 36 days of gestation. Mesodermal structures surround the developing tube, and the circular and longitudinal muscle layers appear at 6 and 9 weeks respectively, the esophageal musculature being a definite structure by 12 weeks of gestation. The developing esophagus is penetrated by blood vessels from the aorta and its branches, and migrating neuroblasts form the myenteric plexus between the muscle layers.

PHYSIOLOGY

The function of the esophagus is to propel ingested material from the pharynx to the stomach. At rest, the esophagus is closed at its upper and lower ends by sphincter mechanisms. The upper esophageal sphincter (UES) prevents the swallowing of air, and the passage of fluid from the gullet to the pharynx. The lower esophageal sphincter (LES) prevents the reflux of gastric contents into the esophagus. Transport through the esophagus takes place in a retrograde direction during vomiting or belching.

Upper Esophageal Sphincter (UES)

The UES is a zone of elevated pressure between the pharynx and the upper esophagus. It is from 2.5 to 4.5 cm in length, and anatomically is composed of the cricopharyngeus muscle. Resting UES pressure is greater than cervical esophageal pressure. Upon swallowing, a contraction is observed in the pharynx. Coincident with this pharyngeal contraction, the UES relaxes to baseline cervical esophageal pressure. These responses are closely coordinated, so that the peak of pharyngeal contraction and the nadir of UES relaxation occur simultaneously. Following deglutition, the UES again contracts to resting UES pressure levels. In the immediate infrasphincteric portion of the esophagus, a peristaltic contraction is seen to begin simultaneously with, or briefly after, UES relaxation. Control of resting UES tone appears to be mediated by pharyngeal branches of the vagal and glossopharyngeal

nerves. Relaxation of the sphincter is a result of inhibition of motor discharges, whereas contraction of the sphincter is the result of motor discharges of the vagus[19].

Esophageal Body

When at rest, i.e., when no deglutition or distention has taken place, the musculature of the esophagus is relaxed, and spontaneous activity does not occur in the normal state. Resting intraesophageal pressure corresponds to negative intrathoracic pressure, being -1 to -2 cm H_2O during expiration, and falling to -12 to -15 cm H_2O during quiet inspiration.

Swallowing elicits a contraction which commences high in the pharynx and continues throught the whole esophagus until it reaches the cardia. This contraction has been termed "primary peristalsis"[20]. The peristaltic wave passes in an aborad direction propelling the bolus of ingested material into the stomach. The contraction wave is usually preceeded by a small, transient drop in pressure. This may be the result of a brief, reflexly-induced inspiratory effect, which, by aspirating air from the upper pharynx may serve to prevent excessive aerophagia; or it may be the result of stretching of the esophagus at the onset of swallowing. This first negative wave occurs within 0.1 sec of swallowing, and lasts an average of 0.4 sec. Next, a small positive wave is seen in 87% of swallows, and is usually attributed to transmission of pharyngeal pressures through the swallowed bolus, and may be more marked with liquid swallows. It occurs 0.5 to 1 sec after

the onset of swallowing, and may occur as a discrete peak, or may plateau into a second small positive wave. This second positive wave is seen in 33% of swallows, usually in the distal esophagus. It is thought to be due to compression of the lower esophageal segment between the advancing bolus and the LES.

The third or main pressure wave is a larger and steeper rise in pressure and represents the peristaltic contraction. The amplitude of this contraction varies according to the site, being in the order of 90 to 100 cm H_2O in the lower esophagus. Duration of the peristaltic contraction is also greatest in the lower esophagus, being in the order of 3 to 5 sec.

The average velocity of propagation of the peristaltic wave is 4 cm/sec, but it varies in different regions of the esophagus. Peristaltic velocity is in the order of 3 cm/sec in the upper esophagus, increases to 5 cm/sec, then decreases to 2.5 cm/sec just above the LES. The peristaltic wave reaches the LES in 5 to 6 sec after swallowing[21].

"Secondary peristalsis" is a term used to describe an esophageal response to local stimulation without the oropharyngeal response. Alternatively, it has been used to describe the initiation of the deglutitive reflex by distension. With the latter definition, there is no difference between primary and secondary peristalsis except in their mode of initiation[22]. The former response may be observed in the striated muscle of the canine esophagus, and is centrally mediated. In the smooth muscle segment of the human esophagus, secondary peristalsis without the deglutitive component has been observed, and is thought to

be a local reflex, and may not require central mediation[23]. Secondary peristalsis is thought to be the mechanism by which material refluxed from the stomach is cleared from the esophagus.

The term "tertiary contraction" is usually used to denote simultaneous, aperistaltic contractions. These spontaneous, simultaneous and often repetitive contractions are usually indicative of a motor abnormality in the body of the esophagus[24].

Lower Esophageal Sphincter (LES)

Fyke, Code and Schlegel were the first to provide conclusive manometric evidence for the existence of a functional sphincter mechanism at the esophogagastric junction[3]. A high pressure zone exists in the distal 2 to 4 cm of the esophagus, which acts as a barrier to retrograde passage of gastric contents into the esophagus. The manometrically observed LES pressure represents both intrinsic sphincter tone and extrinsic pressure from surrounding structures. The sphincter is radially asymmetric in both its length and pressure profile. Symmetry is good in the upper half of the sphincter, but in the lower half, higher pressures are observed on the left side[25]. This asymmetry may be due in part to mechanical factors: the terminal esophagus turns acutely to the left as it enters the stomach; the diaphragm makes an impression on the terminal esophagus which is directed downward and to the right. Intrinsically, it may be due to the

spiral disposition of the circular muscle fibers in the sphincter zone, and/or the action of the gastric sling fibers pulling on the left side of the LES[21].

During stationary pull-through measurements of LES pressure, respiratory variation is observed. In the abdominal segment of the sphincter mechanism, a positive inspiratory deflection is seen, while in the thoracic segment, a negative inspiratory deflection occurs. The point where this shift in respiratory effect occurs has been called the "point of respiratory reversal" (PRR) or the "pressure inversion point" (PIP)[26]. The PIP may be related to the diaphragm, which separates the abdominal from thoracic cavities; thus the PIP may occur at the level of the esophageal hiatus. Indeed, a PIP may be observed if the LES is absent or experimentally destroyed. However, a functioning LES may contribute to the PIP by separating intraesophageal from intragastric pressure[26].

The LES shows rythmic pressure changes that occur at a slow rate of 3 to 4 per min[21]. In addition, phasic elevations in LES pressure related to the migrating motor complex have been described[27].

As the esophageal peristaltic wave reaches the LES, relaxation occurs. LES relaxation occurs 1.5 to 2.5 sec after the swallow is initiated. The LES relaxation may last from 5 to 10 sec; subsequently,

the upper part of the sphincter shows an after contraction which is in continuity with the esophageal peristaltic wave. The post-deglutitive contraction lasts approximately 10 sec, and then LES pressure returns to resting levels. The distal part of the LES does not show an after contraction and the sphincter pressure simply returns to resting levels[21].

Control of Motor Activity

The deglutitive reflex in man is initiated by sensitive areas on the anterior and posterior tonsillar pillars and the posterior wall of the pharynx[28]. Afferents for the deglutitive reflex are carried in the maxcillary branch of the trigeminal nerve, the glossopharyngeal nerve and the superior laryngeal branch of the vagal nerve[29]. The afferent nerves travel to the "swallowing centre", which lies to either side of the mid-line near the inferior olive in the medulla oblongata[30]. The efferents from the swallowing centre activate motor neurons of the cranial nerves that innervate the muscles of deglutition. Normal adults swallow approximately 600 times a day: 200 times while eating, 350 times while awake, and 50 times while sleeping[31].

The oro-pharyngeal phase of deglutition is a highly complex process that involves elevation and forward displacement of the larynyx, with

relaxation of the upper esophageal sphincter; closure of the nasal, oral and laryngeal apertures to channel the bolus in the proper direction; and active propulsion of ingested material from the oro-pharynx to the esophagus. Various medullary centers appear to interact with and modulate each other in a complex manner to integrate these changes[32].

Maintenance of UES tone may be due to passive forces caused by elasticity in the wall[32], or active muscle contraction. Continuous spike activity has been observed in the cricopharnygeus muscle, which is temporarily abolished during swallowing[33]. Tone is maintained by tonic lower motor neuron activity, in mediated via the vagal nerves, and inhibition of tonic activity resulting in UES relaxation is due to central rather than peripheral inhibition[33]. Inhibition of tonic cricopharyngeal contractions is accompanied by contraction of the mylohyoid and other muscles that pull the larynx forward. Thus, UES relaxation is brought about by inhibition of tonic activity in the cricopharyngeus muscle, and UES opening by the actions of the suprahyoid muscles[34].

Contractions of the upper striated muscle segment of the esophagus are dependent upon excitatory lower motor neuron activity, the nerve cell bodies being in the dorsal aspect of the rostral part of the nucleus ambiguus[35]. Peristalsis in this segment is dependent upon the

sequential firing of the lower motor neurons whose axons are destined for various levels of the striated muscle[36], and is abolished by high bilateral vagotomy[32].

Peristalsis may also be initiated by distension of the esophageal striated muscle segment[36] and modulated by both the temperature and volume of the ingested bolus[37,38].

Activation of the swallowing center causes peristalsis in the esophageal smooth muscle segment[38], but peristalsis will still occur after vagotomy[39], suggesting a peripheral regulatory mechanism.

Esophageal smooth muscle exhibits a temporal dissociation between the stimulus applied and the electrical and/or mechanical response[40,41]. A mechanical contraction of esophageal smooth muscle is usually associated with an electrical spike burst, but electromechanical dissociation can occur[42]. Responses of the smooth muscle to stimulation may be divided into intrastimulus and post-stimulus responses. The post-stimulus or "off" response is so called because it occurs after the termination of stimulation[41,42], and is explained on the basis of either a single neurotransmitter hypotheses, or a two neurotransmitter hypotheses[43]. According to the former, a single unknown neurotransmitter is released during stimulation which causes a hyperpolarization of the membrane, which is followed by a

rebound depolarization when stimulation ceases. According to the two neurotransmitter hypotheses, both an inhibitory and excitatory neurotransmitter are released, and upon termination of stimulation, the inhibitory neurotransmitter effect ceases, and the excitatory neurotransmitter then exerts its action[43].

Three types of intrastimulus responses are described: "on", "early", and "duration" responses. The "on" response occurs close to the onset of stimulation, but does not persist for the duration of the stimulus, and appears to be due to direct activation of the smooth muscle[44]. The "early" response occurs some time after the onset of stimulation, and is neurally mediated[45]. The "duration" response begins at the onset of stimulation, continues through its duration, and ceases with the termination of the stimulus[46]. Thus, both the "early" and "off" responses show a latency of response relative to the onset of the stimulus, and either of these responses may be related to the mechanisms of peristalsis in esophageal smooth muscle[41,45]. Further, the latency period becomes progressively longer from proximal to distal esophagus[41], and this latency gradient determines the speed of peristalsis. Thus, when the esophageal smooth muscle is stimulated, a contraction occurs proximally after a short period of latency;

contraction of more distal segments occurs later, owing to the relatively longer latency period, and a peristaltic wave of contractions is propagated in an aboral direction. Neural or local mechanisms may modulate the latency gradient, affecting the speed of peristalsis, or allowing reverse peristalsis in certain situations[42].

The peristaltic wave sweeps over the junctional area of transition from striated to smooth muscle without any indication that different mechanisms are involved. Thus, the centrally regulated latency gradient of the striated muscle segment must be precisely matched with the peripherally regulated latency gradient of the smooth muscle segment, and to-date, very little is known of the mechanism by which this synchrony is achieved[47].

Lower Esophageal Sphincter

The LES is closed in the resting state, providing a barrier to gastroesophageal reflux. The function of the sphincter appears to be controlled by the interaction of three factors: inherent properties of sphincteric smooth muscle, autonomic innervation, and hormonal action.

Smooth muscle of the LES demonstrates specialized responses to drugs, enteric hormones, stretch, and electrical stimulation that differ quantitatively or qualitatively from those of smooth muscle from the

adjacent esophageal body or stomach. *In vitro*, LES muscle strips have a steeper length-tension curve than strips from the esophagus or stomach[48]. This response does not appear to be neurally mediated[48], and thus this sharp rise in tension in response to stretch may represent an intrinsic mechanism of sphincter closure. In humans, LES pressures have been measured using different probe diameters[49]. These studies indicate that tension-diameter curves in the LES are steeper than in the esophagus, and that the diameter at which maximal LES tension develops occurs at a large diameter and not at the diameter of sphincter closure[49]. Thus, the LES muscle can maintain sphincter closure with a minimal expenditure of energy.

This apparently passive response to stretch is not sufficient to explain the genesis of basal sphincter tone. Maintenance of basal tone is an energy requiring process, and the sphincter can be actively relaxed[50]. The LES muscle has a lower resting membrane potential than adjacent esophageal and gastric smooth muscle[51], and *in vitro* observations suggest that this partial depolarization is due to an inward calcium leak, which may activate myofibrils and cause tonic LES contraction[52].

Current evidence suggests that the LES is innervated by excitatory cholinergic[53,54] and adrenergic[55] nerves. The precise role of

cholinergic stimulation in regulation of sphincter tone in humans remains to be clarified, as vagotomy in man does not reduce sphincter pressure[56]. The mechanism controlling normal sphincter relaxation during swallowing also remains unclear[57]. Efferent inhibitory fibers have been demonstrated in the vagal nerves of the opossum[58]. However, vagotomy does not abolish sphincter relaxation in either animals[59] or man[60]. The cell bodies of the inhibitory nerves are believed to be located in the esophageal plexuses, and the preganglionic fibers arrive via the vagal nerves[58]. Ganglionic transmission is cholinergic, but the identity of the post-ganglionic inhibitory neurotransmitter is not known[61].

Many hormones, particularly gastrin, have been shown to affect LES pressure[62], and gastrin was initially considered to be the major regulator of LES tone. Subsequent studies cast doubt on these findings[63], but it may be that gastrin modulates changes in LES pressure after meals[64].

Secretin, cholecystokinin, glucagon and insulin have been shown to affect LES pressure, but the precise interplay of these hormones and the full significance of the physiologic roles of any or all of these hormones has yet to be determined[57].

THE ANTI-REFLUX MECHANISM

A positive pressure gradient exists between the abdominal and thoracic cavities, and this gradient increases substantially during exercise, coughing, stooping and other events associated with abdominal muscle contraction, changes in gravitational position, or both. Thus, without some protective mechanism, GE reflux would occur continuously. Further, a mechanism that normally prevents reflux must allow entry of an esophageal bolus into the stomach after swallowing and allow egress of gastric contents during vomiting or belching. Factors proposed to explain the anti-reflux mechanism are a) anatomic mechanical factors, which are mainly extrasphincteric and b) intrinsic LES tone.

Prior to the demonstration of a physiologic sphincter mechanism[3], anatomic factors were thought to be soley responsible for the prevention of reflux. Despite earlier reports of areas of anatomical muscle thickening in the lower esophagus[29], the consensus of opinion to-date is that there is no anatomical basis for an intrinsic sphincter mechanism,[65,29]. Many extrasphincteric mechanical factors have been described that are thought to contribute to the closing mechanism. Possible valve mechanisms include: a mucosal flap[66], a flutter valve[67], an acute esophagogastric angle[67], and the gastric sling fibers[68]. A second group comprises mechanical factors which may cause esophageal compression at/or near the diaphragmatic hiatus. These include a pinchcock action of the diaphragm[69], a hepatic tunnel, a sling action of the right crus, an esophagogastric "joint"[70], and the

phrenoesophageal membrane[13]. An intraabdominal segment of esophagus is thought to assist sphincter closure by being surrounded by a positive pressure environment[71], and indeed restoration or maintenance of such a segment is considered by many to be an important aspect of anti-reflux surgery[72,73]. The mucosal choke hypothesis[70] proposes that during sphincter closure, adhesive forces which resist sphincter opening exist between interdigitating mucosal folds.

Another important characteristic of the LES is its ability to increase its pressure in response to increased intraabdominal pressure. This effect was initially attributed to the mechanical action of passive squeeze on the intraabdominal portion of the sphincter[3]. However, LES pressures developed in response to compression usually exceed the rise in intragastric pressure[74,75], and this response is inhibited by atropine and vagotomy[76,77]. A similar response is seen in patients with hiatal hernia, whose LES is therefore surrounded by intrathoracic pressure[78]. Other studies suggest that the mechanism by which the sphincter responds to increased intraabdominal pressure involves a more complex interplay of neural and external mechanical factors[79]. The radial asymmetry observed in the pressure profile of the LES may be due to extrinsic or intrinsic factors, as discussed above[18,22].

The intrinsic physiologic properties of the sphincter have been discussed. The opinion of most recent reviewers[4,7] is that evidence currently available does not warrant the conclusion that intrinsic LES strength is the sole barrier to GE reflux, and that many mechanical

factors serve to augment the anti-reflux barrier provided by the intrinsic LES. The precise interplay between these extrinsic and intrinsic factors has yet to be determined.

CONSEQUENCES OF GASTROESOPHAGEAL REFLUX

Reflux of gastric contents into the esophagus has been shown to occur in normal asymptomatic subjects[80,81]. However, these episodes occur with a higher frequency and for a longer duration in patients with significant symptoms. Prolonged exposure of the esophagus to gastric juice may result in disabling symptoms; may damage the esophageal mucosa as evidenced by inflammation, ulceration, stricture formation, and bleeding; or may lead to epithelial changes in the esophagus, with a malignant potential[82].

Gastroesophageal reflux has only become clearly recognized as a disease entity since the early part of this century. Much confusion arose over the association of hiatal hernia with reflux disease. Prior to 1900, hiatal hernia was regarded as an anatomical curiosity, and Bowditch, writing on the subject in the mid-nineteenth century commented that most observers were ignorant of the true nature of the condition, "their modes of treatment have been entirely empirical and generally very absurd, and not a few times absolutely hurtful to the patient"[83]. He also felt that as the disease was so rare, few surgeons would have the opportunity to operate upon it more than once or

twice in the course of a working lifetime.

Not until the turn of the century, with the advent of contrast radiology, was a diagnosis of hiatal hernia in living patients made possible[29]. Then, for several decades, hiatal hernia was classified with other types of diaphragmatic hernia, and was felt to pose the same threat of incarceration, strangulation and perforation as do other forms of herniae. In his paper "Peptic Esophagitis: a new clinical entity" in 1935, Winklestein was perhaps the first to recognize that inflammatory changes in the esophagus were due to the action of gastric juice[84]. Allison, in 1945, clearly established that gastroesophageal reflux was the cause of the symptoms and pathology that frequently accompany hiatal hernia and was the first to use the term "reflux esophagitis"[85,86]. In his "Anatomy of Repair" in 1951, Allison described an operation for the prevention of reflux based upon restoration of normal anatomical relationships[86]. Unfortunately, in several centers, more than one-third of the patients undergoing this operation were later reported to have peristence of reflux even though the hiatal hernia might have been corrected on postoperative radiographic examination[1]. Several reports have since attested to the occurrence of severe gastroeosphageal reflux disease without hiatal hernia, and of hiatal hernia without reflux disease[88,89,90]. Thus, history has repeated itself and hiatal hernia of the sliding variety, unless accompanied by reflux, is once again nothing more than an incidental curiosity.

Clinical Presentation

The classical symptoms of GE reflux disease are heartburn and regurgitation evoked by bending over or lying flat, and relieved by adopting an upright posture. To this may be added prompt relief of symptoms with antacid therapy. Most people have, at one time or another, experienced heartburn, and there is a wide spectrum in the frequency and severity of symptoms. Heartburn is defined as a burning sensation in the epigastric and lower substernal regions occurring during or within an hour or so after meals, or accompanying the ingestion of irritating foods, e.g., very hot or very cold drinks, alcohol, highly spiced foods. It frequently radiates upwards along either costal margin, more often the left, and may be induced by those measures as raise intra-abdominal pressure[14,91].

Heartburn is often accompanied by regurgitation of sour, acidic material into the mouth, and the combination of these symptoms is pathognomonic of G.E. reflux disease, particulary if symptoms are aggravated by postural change. Sleep is often disturbed, and many patients experience symptoms when lying supine or on the right side, but not on the left.

Some patients present with pharyngeal symptoms, and have often had psychiatric consultations for "globus hystericus"[14]. Some may experience pain radiating to the cervical spine, both rami of the mandibles, or ears. A number of patients present hoarseness, chronic cough, or chronic pharyngitis, and may initally consult with an otolaryngologist. Some patients present with symptoms remarkably

similar to angina pectoris, and as both conditions are being recognized with increasing frequency, differentiation is extremely important[14].

Other than the classical symptoms of heartburn and regurgitation, patients with complicated G.E. reflux disease may experience dysphagia, odynophagia, and pulmonary symptoms. Dysphagia is almost universally noted in patients who have developed an esophageal stricture due to reflux. It is most important to outrule other causes of dysphagia, such as neoplasm. Dysphagia may also occur in patients with esophagitis but no stricture, and indeed in patients with no esophagitis at all. Episodes of reflux may trigger esophageal spasm or tertiary contractions which may cause dysphagia in patients without esophagitis. It must also be noted that dysphagia due to stricture may be the presenting symptom of G.E. reflux disease. Thus, symptoms are not a reliable guide to the severity of the pathological process, and even those patients with mild symptoms suggestive of GE reflux should be thoroughly investigated[14].

Aspiration of regurgitated material into the lung is another serious complication of GE reflux disease, and pulmonary symptoms may be the major presenting complaint. Thus, any patient with a chronic unexplained cough, particularly if nocturnal, or chronic basal inflammatory changes, should be investigated for GE reflux disease[92].

Chronic blood bloss may result from esophagitis, resulting in anemia. Blood loss, if it occurs, is usually minor. Rarely, however, patients may bleed massively from diffuse esophagitis, or from a chronic penetrating ulcer in a segment of esophagus lined with ectopic gastric mucosa. Erosion of esophageal varices by esophagitis in patients with reflux must be considered in the differential diagnosis[93,94].

PATHOLOGY

The term "reflux disease" has replaced the term "reflux esophagitis" in describing this condition as it is now recognized that severe clinical symptoms which incapacitate a patient may occur without endoscopic evidence of esophagitis; and that a patient who has never had significant symptoms may present with a reflux induced stricture. Thus, the spectrum of morphological change ranges from a normal esophageal mucosa, to erythema and friability of the mucosa, to esophagitis with superficial erosions, or deeper chronic ulceration, and finally, fibrosis with stricture formation[14].

The histological features of esophageal ulceration were first described by Quincke in 1879[95]. Until recently the histological criteria for "esophagitis" were those of the inflammatory process, namely hyperemia, edema, infiltration with neutrophils, lymphocytes and plasma cells, and fibrosis. Epithelial erosion and ulceration may be present; the inflammatory reaction may be limited to the outer part of the lamina propria or may extend into its deeper layers or even into the muscularis mucosae[96,97].

Ismail-Beigi, Horton and Pope, in 1970, described new histological criteria for the assessment of earlier changes which take place predominantly in the epithelial layers[98]. They described a thinner surface layer of squamous cells. The papillae are elongated and more vascular, and may reach the mucosal surface. The basal or germinative layer is hyperplastic, and may occupy from 50% to 80% of the full thickness of the epithelial layer. The basal cells contain more

nucleii. It would appear, therefore, that as surface cells are lost due to the action of local irritants, the basal layer compensates to produce a faster turn over of cells.

If the rate of loss of cells from the luminal surface exceeds the rate at which they can be replaced, superficial esophagitis develops with accompanying acute and chronic inflammatory changes. In patients with severe reflux changes, Behar and Sheahan (1975) found polymorphonuclear leucocytes in 40% of esophageal biopsies[99]. Chronic inflammatory changes with lymphocytic and monocytic infiltration have been described in 55 to 85 percent of patients with reflux sysmptoms[96]. In severe esohagitis, superficial ulcerations, which rarely extend through the muscularis mucosa and tend to re-epithelialise rapidly, are frequently found. On the other hand, more extensive ulceration produces an inflammatory and fibrotic reaction that may extend through the entire esophageal wall and even into the surrounding mediastinum[100].

In 1950, Barrett called attention to patients in whom the distal one-third to one-half of the esophagus is lined by columnar epithelium, rather than the normal stratified type[101]. This columnar epithelium usually has all the histological characteristics of the mucus secreting columnar epithelium of the cardia of the stomach, and even on occasion may contain parietel and chief cells. Originally, it was postulated that these columnar cells represented embryological remnants, as the embryonic esophagus is first lined by columnar epithelium which is replaced by squamous epithelium in the fifth to sixth month of gestation. It is now well established, however, that this heterotopia

is an acquired abnormality and represents a serious complication of gastroesophageal reflux disease[102]. It is not quite clear why an area of esophageal ulceration should be repaired in some instances by columnar rather than squamous epithelium. One explanation is that the columnar epithelium of the cardia is more resistant to acid-peptic digestion, and hence has a growth advantage over squamous epithelium. An alternative suggestion is that the columnar epithelium may originate from outgrowths of the esophageal submucosal glands rather than as a direct extension from the cardia[96]. It is even less clear why severe esophagitis should lead to stricture formation in some patients and columnar epithelialisation in only a few. This lesion assumes even greater significance when it is realized that adenocarcinoma of the esophagus may arise in up to 10% of patients who have a lower esophagus lined with columnar epithelium[82].

In addition to acute, subacute and chronic esophagitis, chronic localized penetrating ulceration of the esophagus can occur. Usually described as peptic ulcers of the esophagus, these lesions are usually single and discrete, and are usually located on the anterior or posterior wall. Occasionally, two ulcers will be found on opposing walls. The histological features of these ulcers exactly resemble those found in chronic peptic ulcers of the stomach, and they always occur in or very near to glandular mucosa. When a peptic ulcer is found in the esophagus it is almost invariably accompanied by adjacant superficial esophagitis of the squamous mucosa[96,101].

PATHOPHYSIOLOGY

The lower esophageal sphincter is now regarded as the main barrier to reflux. Nevertheless, many patients with GE reflux disease have LES pressures in the normal range, and it has been shown that reflux episodes occur in normal subjects. These observations suggest that manifest GE reflux disease may be the result of many contributing factors. Thus we must consider those factors that normally prevent reflux, and the mechanisms by which reflux occurs; those factors that normally protect the esophagus from the injurious effects of refluxed material; and those factors that influence the volume and composition of the refluxed material[4,7].

There is generally a poor correlation between resting LES pressure readings and clinical evidence of GE reflux disease[103,104]. Recent studies by Dent *et al.* have shown that basal LES pressures vary considerably throughout the course of the day, both in normal subjects and in reflux patients[105]. Overnight studies during which LES pressure and esophageal pH were continually monitored, indicated that GE reflux may occur by any of three general mechanisms. Transient inappropriate relaxations of the LES may occur that are not related to swallowing. These were most frequently seen when resting LES pressure was in the normal range, and accounted for 98% of the reflux episodes observed in normal subjects. In subjects with a hypotonic LES, episodes of reflux were seen to occur during transient rises in intra-abdominal pressure. In subjects with a feeble or atonic LES, episodes of spontaneous free GE reflux occurred. Among symptomatic patients, two-

thirds of the reflux episodes observed occurred during transient inappropriate LES relaxations, with the remaining third divided between the mechanisms of transient increases in intra-abdominal pressure and free reflux. The first mechanism predominated in those patients with LES pressures in the normal range, and the latter two mechanisms predominated in those patients with a persistently low LES pressure. The mechanism of transient inappropriate LES relaxations appears to explain the apparent paradox of how GE reflux occurs in normal subjects and in those reflux patients with a normal LES profile[105].

Many hormones are known to affect LES pressure, and diminished release of endogeneous gastrin or LES insensitivity to gastrin were suggested as possible causes of the low LES pressure often seen in reflux patients. Subsequent studies, however, have not confirmed this "gastrin hypothesis", as it became known, and fasting serum gastrin levels were found to be similar in reflux patients and control subjects and a correlation between fasting serum gastrin levels and LES pressures could not be shown[62,63,64].

The most clinically important hormonal action on the sphincter is probably that produced by progesterone. LES pressures are progressively decreased during pregnancy, are decreased in women taking progesterone-containing anovulants, and are even decreased in the luteal phase of normal menstrual cycles[106,107]. This probably accounts for the high incidence of heartburn during pregnancy. Secretin, cholecystokinin and glucagon decrease LES pressure in pharmacological doses, and certain prostaglandins reduce LES tone[108,109,110,111].

Alteration of the normal anatomy of the gastroesophageal junction may result in a decreased LES pressure. An abnormal phrenoesophageal ligament insertion[13], an absent intra-abdominal segment of the esophagus[73], or a hiatal hernia may result in a mechanical disadvantage to normal sphincter function[12]. Low LES pressures have been found in the aged. Foods such as fats and chocolate diminish LES pressure as do drugs such as theophylline, alcohol, nicotine and nitroglycerine[112,113,114]. An intriguing suggestion is that reflux per se may cause a fall in LES pressure, as observed when esophagitis was induced experimentally in cats[115,116].

The mechanisms by which the esophagus is normally protected from the injurous effects of refluxed material include the tissue resistance of the mucosa, the actions of saliva and esophageal gland secretions, and the ability of the esophagus to clear the refluxate[4]. The esophageal mucosa is quite sensitive to damage from acid, pepsin, or bile salts, and the degree of resultant damage may depend upon the speed at which the squamous epithelium regenerates. When the surface layer of the epithelium is damaged, the permeability of the mucosa to hydrogen ion is increased, and transmucosal potential differences are altered[117,118,119,120,121].

Saliva is rich in bicarbonate, which buffers acid, and sulphated polysaccharides, which have antipeptic properties. As the secretions of the esophageal submucosal glands are scant, swallowed saliva may have an important protective role[6,122].

The length of time that refluxed material remains in contact with the esophageal mucosa may be of paramount importance in producing

disease[4,123]. Studies employing 24 hr esophageal pH monitoring have shown that the duration of reflux episodes is increased in patients with reflux disease and that severity of symptoms correlates well with contact time[124,125,126]. Esophageal clearance depends upon gravity and upon esophageal peristalis; in the recumbent position, the effect of gravity is removed. Acid clearance time, as determined by the number of swallows taken to restore normal pH following the instillation of acid into the esophagus, is prolonged in patients with GE reflux[4,127,128]. Motor disorders in the distal esophagus have been reported in patients with severe esophagitis or stricture[129,130,131,132]. As reflux may induce a fall in LES pressure[115,116], the concept has arisen that reflux may induce impairment of esophageal peristalsis and clearance, thus setting up a self-perpetuating cycle[4,6,7]. Conceivably, an episode of reflux may produce acute injury resulting in impaired peristelsis and clearance, which in turn produces a fall in LES pressure, allowing more reflux to occur. This hypothesis is supported by animal experiments in which acid was instilled into the mid esophagus of both cats and baboons resulting in significant decreases in LES pressure and decreases in peristaltic amplitudes in the distal esophagus[115,116,133]. To date, there has been no concrete evidence to support this hypothesis in humans.

The volume and composition of the refluxed material may influence the course of events should reflux occur. From this perspective, the stomach plays a major role in the pathogenesis of reflux disease. The volume of fluid in the stomach is a function of ingestion, gastric secretion, gastric emptying, and duodenogastric reflux. Delayed gastric

emptying has been reported in up to 40% of reflux patients[134,135]. Thus, more volume is available for reflux into the esophagus. Gastric acid secretion is normal in reflux patients[136,137]. Increased duodenogastric reflux, as demonstrated radiographically, and by increased concentrations of bile salts in the gastric aspirate, may play a role in the pathogenesis of GE reflux disease[138,139]. Not only would duodenogastric reflux increase the gastric volume available for GE reflux, but would also place high concentrations of bile salts in the stomach from which they could reflux into the esophagus[6]. Impaired antral motility, and an increased incidence of antral gastritis has been reported in patients with GE reflux[140,141].

In summary, some defect in the LES allows reflux to occur. The volume and composition of the refluxed material depends upon functions of the stomach and perhaps of the pylorus, and the effect the material has upon the esophagus depends not only on the contents of the refluxate, but also upon the defence mechanisms of the esophagus itself. Cyclic mechanisms may then occur which allow perpetuation of this process once it has begun.

DIAGNOSIS

The evaluation of suspected GE reflux should include a careful clinical history and the appropriate use of specialized clinical tests. A classical symptom complex and a rapid response to conventional therapy leave little doubt as to the diagnosis. However, on occasion, GE reflux may produce an atypical clinical picture and the response to therapy may be unsatisfactory. Primary motor disorders of the

esophagus, and cardiac, biliary and gastroduodenal disorders are frequently associated with symptoms which are difficult to distinguish from those of reflux. A multitude of tests are currently available to evaluate these patients, and are discussed below. Unfortunately, no single test has yet been accepted as the standard for diagnosis of GE reflux disease, and a carefully selected combination of tests must often be employed.

Diagnostic tests for GE reflux disease may be classified as follows:

1. Tests of LES competence. LES competence is assessed by manometric measurements of resting LES pressure and by measuring the response of the sphincter to compression.

2. The acid perfusion test of Bernstein is a test of esophageal sensitivity to acid, and is useful in deciding if symptoms are attributable to the esophageal disease.

3. Tests that evaluate esophageal damage. These include double-contrast radiography, potential difference measurements, endoscopy, biopsy, acid clearance test, and manometric evaluation of esophageal peristalsis.

4. Tests that demonstrate the presence of reflux. These include radiography and water-siphon tests, long and short-term pH monitoring, the common cavity test, and esophageal scintigraphy.

Esophageal Manometry

Esophageal manometry allows measurements of LES pressure to be made both at rest, and in response to raised intra-abdominal pressure; allows a study of the deglutitive response of the sphincter; allows an assessment of esophageal peristaltic activity, and, where appropriate, an examination of the upper esophageal sphincter.

The first manometric motility studies of the gastrointestinal tract were performed by Kronecker and Meltzer in the 1880's, who used air-filled balloons as pressure transmitters[142]. Water-filled balloons were in use since the 1940's, but because of inaccurate and delayed assessment of rapid pressure changes, dependence of sphincter pressure measurements on balloon diameter, and the effect of the balloon on motility, balloon kymography was abandonded[142].

The 1950's saw the introduction of water-perfused catheter systems, which transmitted pressure to extracorporeal pressure transducers (e.g., Stratham-transducers). It transpired in the 1960's that only by using constant perfusion rates could accurate and reproducible quantitative results be obtained[143,144,145,146]. However, high perfusion rates led to inaccuracy of measurements[146], and a further advance was made by the introduction by Arndorfer et al. in 1977 of a hydraulic-capillary infusion system[147], which allowed improved quantitative measurements of both LES pressure and esophageal peristaltic waves.

The clinical disadvantages of perfusion manometry include the need for an exact motorized perfusion device, hydraulic artefacts, the need for catheter disinfection, and a catheter compliance which cannot be completely eliminated. Many forms of intracorporeal microtransducers

have been developed, but nearly all have a low mechanical resistance to repeated use, and have thus not found wide acceptance for routine clinical purposes[148].

In current clinical practice, esophageal manometry is used primarily to assess LES pressure. Dodds et al., reviewing reflux disease in 1976[65], stated that "this practise is based on the widely accepted notion that resting LES pressure correlates directly with sphincter competency. Regretably, most investigative studies of reflux patients make no reference to esophageal body motor activity".

Earlier studies, using non-infused catheter systems, could show no separation on the basis of LES pressure between normal subjects and those with reflux symptoms. With the advent of perfused catheter systems, there initially appeared to be a clear separation between control subjects and patients[143,144,145]. Later studies with larger numbers of patients showed considerable overlap in LES pressure readings between control subjects and reflux patients[149,150,151,152,153]. A review by Richter and Castell in 1982[7] found that an LES pressure less than 10 mmHg has poor sensitivity (58%) but good specificity (84%). Others feel that a reliable discrimination of a reflux patient can only be made with a resting LES pressure of less than 6 mm Hg[4,153]. Some correlation, however, exists betwen resting sphincter pressure measurements and the morphological severity of disease, patients with severe esophagitis having lower pressures than those without[155].

Although a poor sphincter response to raised intra-abdominal pressure has been reported in reflux patients[88,156], the value of this measurement as a diagnostic test for reflux disease has not been

assessed. All recent reviews attest to the poor sensitivity of resting LES measurements, and Castell suggests that routine measurement of resting LES pressure is impractical[7].

The Acid Infusion Test

The acid infusion test[157] is widely accepted as a clinical test for diagnosing GE reflux disease. Castell[7] reviewed seven series, and found an overall sensitivity of 79% and a specificity of 82%, while Dodds et al.,[65] conclude that high false-positive and false-negative rates make the test non-specific. Different criteria for interpretation may account for these differences[158]. Benz et al.[150] concluded that the acid infusion test showed the greatest degree of correlation with other standard tests for GE reflux. It must be remembered, however, that it is a test of esophageal sensitivity to acid, and perhaps its major clinical usefullness is in determining whether symptoms are produced by the esophagus.

Radiographic examination

Many patients with GE reflux disease have a hiatal hernia on barium X-ray examination, but so do 50% of the population over 50 years of age[159]. Neither does the absence of hiatal hernia rule out reflux disease[87,88,89]. Flouroscopy or cineradiography after gastric loading with barium is a poor test for reflux, with a sensitivity of 40% and specificity of 85%[7,160]. The "water siphon" test[161] has a high number of false positive results[7]. Acid-barium swallows[160] have shown 62% false positive and 40% false negative rates[150]. Double

contrast radiography[162] is relatively insensitive to mild degrees of esophagitis, but has a sensitivity and specificity approaching 100% with severe degrees of inflammation, and shows good correlation with endoscopic findings of severe esophagitis, ulcer, or stricture[163]. Thus, radiographic techniques have both poor sensitivity and poor specificity in diagnosing GE reflux disease, but are useful in determining whether significant complications have occurred, and in outruling other upper gastrointestinal pathology.

Endoscopy

Severe symptomatic reflux disease can occur without the presence of endoscopic esophagitis[14]. Thus, although endoscopy is highly accurate in diagnosing esophagitis, the absence of gross change does not outrule the diagnosis. There is agreement about the finding of moderate to severe esophagitis (grades II and III), which include: superficial ulcers or erosions; hemorrhagic mucosa with exudates; deep, punched out esophageal ulcers; and esophageal strictures[164]. When these are present, endoscopy has a diagnostic specificity of 96%, but a sensitivity of only 68%[151]. Interpretation of mild or grade I esophagitis is difficult, and the findings are non-specific[7].

Biopsy

Ismail-Beigi *et al.* described reparative changes in the esophageal mucosa which offered improved histologic criteria for the diagnosis of GE reflux disease[98]. These changes include basal layer hyperplasia and papillary elongation, with loss of surface epithelial cells. In

both the original series, and in Behars series in 1976[164], both a sensitivity and specificity in the order of 90% was reported. However, in 1975, Weinstein, Bogoch and Bowes[165] examined mucosal suction biopsies from asymptomatic control subjects and found similar changes in 57% of biopsies in the distal 2.5 cm of esophagus and in 19% of the biopsies above this level, indicating a much lower specificity than otherwise believed. Ismail-Beigi et al. found frank histologic features of inflammation in only 18% of their series; other studies have shown inflammatory infiltrates in up to 40% of biopsies[99,164]. Thus, biopsy findings found positive by Ismail-Beigi's criteria may have a much lower specificity than here-to-fore believed, especially if taken from the distal 2.5 cm of the esophagus.

Esophageal pH monitoring

In 1958, Tuttle and Grossman introduced the use of a pH electrode in the esophagus to detect reflux of acid from the stomach[166]. This was refined by Skinner and Booth[167], who developed the Standard Acid Relfux Test. This involves loading the stomach with 300 ml of 0.1 N HCl, and, Castell, reviewing eight studies, found an overall sensitivity of 84%[7]. However, in a recent study, no false positive results occurred with up to 100 ml acid loading, but 37% and 50% false positive responses occurred with 300 ml and 500 ml acid loading[168]. Without acid loading, short-term pH monitoring shows poor sensitivity (40%) but excellent specificity (99%)[151,169].

Since 1974, Johnson and DeMeester[124] have popularized 24 hr pH monitoring of the distal esophagus. The available literature suggests

that this test has excellent sensitivity (88%) and specificity (98%) for GE reflux disease[7]. It has also proved an excellent investigative tool in researching the pathogenesis of reflux disease[105,125]. However, expense and the need for hospitalization and time factors ensure that in the routine clinical sense this test will be reserved only for the most difficult diagnostic problems.

The Common Cavity Test

Described by Butterfield in 1972[170], this is a manometric test that measures intraesophageal pressure while compression is applied to the abdomen. If a rise in intraesophageal pressure occurs, indicating a "common cavity" between stomach and esophagus, it indicates sphincter incompetence. Butterfield found no positive results amongst 14 control subjects, but found marked rises in intraesophageal pressures in his group of 13 symptomatic patients. Some observers have since observed a high false positive rate[4], but the common cavity test has not been evaluated adequately since its original description.

Gastroesophageal Scintiscanning

Described by Fisher *et al.* in 1976[171], this test consists of loading the stomach with Technetium^{99M} Sulphur Colloid in 300 ml of normal saline, and counting scintillation over the esophagus and stomach with a gamma camera. Abdominal compression is applied to induce reflux. Fisher reported a 90% sensitivity and 90% specificity for this test. However, Hoffman *et al.* in 1979 found a positive scintiscan in only four out of 29 reflux patients[172]. The appeal of this test is its non-invasive nature, and it may become a good screening test for GE reflux, particularly in children[7].

Treatment of GE reflux

Medical Therapy

In his review article[7], Castell has outlined a therapeutic approach to the patient with GE refux disease. General measures include regular meals, avoiding food or beverages for four hours before bedtime, weight loss if obese, and elevation of the head of the bed. Smoking should be discontinued, and alcohol, fats, chocolate, citrus fruits and spicy foods should be avoided. Certain medications will decrease LES pressure, such as progesterone, theophylline, propranolol, and diazepam, and are best discontinued if possible. Antacids generally produce prompt symptomatic relief, and are effective in controlling mild to moderate symptoms.

Other than antacids, specific medications that are available are bethanechol, metoclopramide, and cimetidine. Bethanechol is a cholinergic agent that has been shown to increase resting LES pressure, decrease GE reflux, and improve esophageal acid clearance. It appears to promote healing of esophagitis and decrease antacid use, and seems well tolerated[173,174]. Metoclopramide has been shown to increase resting LES pressure, and to improve the antral motility and gastric emptying abnormalities present in some patients with GE reflux disease[175,141]. However, up to one third of patients experience neurologic or psychotropic side effects and must discontinue the drug. Cimetidine acts by reducing gastric acid concentration, and has no direct effect on LES pressure[7]. Although cimetidine appears to effectively relieve symptoms, significant healing of esophagitis has not been documented[176,177]. Alginates seem to be effective in the treatment of GE reflux, but are probably not better than antacid

therapy[178].

Thus, the medical treatment of all patients with GE reflux disease should include general postural and dietary measures, avoidance of nicotine and potentially harmful medications, and specific therapy with antacids or alginic acid. More severe or unresponsive cases should have cimetidine with bethanechol or metoclopramide added to their regimes. Between 5% and 10% of GE reflux patients will fail to respond to the best in medical therapy, and warrant a surgical antireflux procedure[7].

Surgical treatment

Until the late 1950's, surgeons working in this area concentrated upon anatomical correction of hiatal hernias. Symptoms were poorly understood, and no consideration was given to reflux[14]. Harrington in 1928 was amongst the first to report on a series of diaphragmatic hernia repairs[179]. Allison, in 1951, recognized the association of symptoms with reflux, and emphasized the importance of anatomical correction of the cardia in preventing reflux[86]. Collis (1954) and Boerema (1955) sought to create an intraabdominal segment of esophagus by anchoring the gastroesophageal junction beneath the diaphragm with sutures to the anterior or posterior abdominal wall [180,181]. In 1955, Nissen and Belsey, working independently, developed the principle of wrapping a portion of the proximal stomach around the distal esophagus to complement anatomical repair of the hiatus, and this principle remains the cornerstone of surgical prevention of GE reflux[5,182]. Hill introduced the posterior gastropexy operation in 1960 and modified it subsequently to include calibration of the cardia[183,184].

In current surgical practice, the most widely used anti-reflux operations are the Nissen fundoplication, the Belsey Mark-IV repair and

the Hill posterior gastropexy with calibration of the cardia. The basic surgical principles of these procedures are similar: each involves mobilization of the distal four to six cm of the exophagus; each involves to some degree the creation of a flap-valve or wrap of gastric fundus onto the distal esophagus; and each involves narrowing of the margins of the hiatus with sutures. The Nissen and Hill procedures use a transabdominal approach, while the Belsey operation requires a transthoracic approach.

Current evidence suggests that the Nissen fundoplication affords the most permanent symptomatic relief. DeMeester et al, 1974, reported on a randomized prospective trial of 45 patients with GE reflux disease[185]. Fifteen patients had the Hill procedure, 15 the Belsey procedure, and 15 the Nissen procedure. Symptomatic relief was obtained in 47% of those undergoing the Hill repair, 80% of those undergoing the Belsey repair, and 100% undergoing the Nissen repair. Objective post-operative evidence of reflux, as assessed by radio-graphic examination, standard acid reflux test, 24-hr esophageal pH monitoring, and esophageal monometry showed that the Nissen repair gave the most satisfactory results of the three procedures[185]. Others have also found the Nissen fundoplication to be superior to the Belsey operation both in terms of symptomatic relief and objective evidence of reflux[186], and most reports evaluating the Nissen repair attest to its low morbidity and mortality, good patient tolerance, and long-term efficacy in preventing GE reflux[187,188,189,190,191,192].

A number of specific complications have been described following a valvuloplasty of the Nissen type. While many of these are rare, the "gas-bloat" syndrome and post-operative dysphagia are frequent complications, particularly on a short-term basis.

Described by Woodward in 1971, the "gas-bloat" syndrome is characterized by post-prandial fullness, inability to belch or even vomit, increased amounts of flatus, and meteoristic bloating of the abdomen[193]. Acute post-operative gastric dilatation may occur, requiring the prompt passage of a naso-gastric tube[194]. It occurs more frequently after the Nissen fundoplication[195], and incidences of 20% to 30% have been reported[196]. While the "gas-bloat" syndrome may be due to post-operative supercontinence of the cardia[197], inadvertent vagotomy may contribute to gas-bloat like symptoms, diarrhea, and gastric retention[185,198]. Use of a purposefully wide cuff may prevent gas-bloating[196,199].

Post-operative dysphagia occurs in 10% to 15% of patients undergoing fundoplication[198], the most important cause being a narrow cuff. It may also be caused by inhibition of cranial movement of the cardia during swallowing[185], or by an increased incidence of tertiary contractions in the distal esophagus due to denervation[194]. Symptoms usually disappear spontaneously within three to four months, but occasionally bouginage may be necessary[198].

Telescoping is a rare complication of fundoplication, and is more likely to occur if a proximal gastric vagotomy is conducted at the same time[200,201], and is similar to the "slipped" fundoplication[202]. Indicental splenectomy due to iatrogenic injury is occasionally indicated but adds considerably to the post-operative morbidity[203]. Gastric ulceration after fundoplication has been reported, and may be due to vagal nerve entrapment[204]. Other documented complications include complete or partial disruption of the wrap-around, intussusception of gastric mucosa cephalad to the fundoplication, and gastric ulcer with gastro-bronchial fistula[205].

The mechanism by which fundoplication exerts its action in preventing GE reflux remains controversial. Many studies have reported an increase in lower esophageal sphincter pressure following anti-reflux surgery, the highest pressures being recorded after the Nissen procedure[185,186,189,197]. Improved response of the sphincter to abdominal compression has also been reported[185,206], suggesting a restoration of "physiological" sphincter function post-operatively. However, autopsy studies have shown that fundoplication can prevent artificially induced reflux in the cadaver[207]. Bowes and Sarna, in 1975, observed no improvement in the sphincter response to abdominal compression post-operatively and described incomplete relaxation of the sphincter in resonse to deglutition[208]. Extrinsic compression of cadaver esophagus produced a zone of elevated pressure. Bowes et al concluded that increases in sphincter pressure after fundoplication are probably secondary to extrinsic narrowing and do not constitute evidence that a physiological sphincter has been created[208].

The effects of fundoplication on the motor function of the esophageal body have been poorly documented. Skinner describes an increased incidence of tertiary contractions in the distal esophagus in patients with post-operative dysphagia, and presumes they are due to irritation from dissection and tension on teh repair[194]. Hill has described a motor abnormality consisting of simultaneous, aperistaltic, low amplitude contractions with poor esophageal propulsion[205], which he considers is specific to the Nissen fundoplication, and which disappears when the repair is converted to a posterior gastropexy. He feels that this may be due to the esophagus having lost its distal attachment and being accordioned on itself and being unable to produce sequential waves without distal fixation.

If GE reflux is complicated by a stricture, or a shortened esophagus, it may prove necessary to complement an anti-reflux procedure, and most authors prefer the Collis gastroplasty with fundoplication[1,209] to the Thal patch procedure[1,210]. Occasionally, local resection of the stricture and colonic replacement of the resected segment will be required[211].

Angelchik, in 1979, described the use of a ring-shaped silicone prosthesis for the treatment of GE reflux, but it has met with little or no enthusiasm and at times frank condemnation from the surgical academic sector[212]. A recent study suggest that it is safe, simple, reproducable, and can eliminate the symptoms and signs of GE reflux[213]. However, the widespread use of this device must await the oucome of randomized prospective trials. Until such time the weight of evidence in the literature is that the Nissen fundoplication if performed with attention to technical detail, is safe, simple, and can fulfill the five criteria for an acceptable anti-reflux technique as recently ouitlined by Belsey, namely: 1, should achieve complete and permanent relief of all symptoms; 2, should restore the patients ability to lead a normal and satisfactory life without further medical, dietary or postural treatment; 3, should retain the ability to "belch"; 4, should retain the ability to vomit; and 5, should allow objective proof by pH electrode or other laboratory studies that the reflux has been completely controlled[214].

OBJECTIVES OF PRESENT STUDY

The limitations of manometric recordings of lower esophageal sphincter pressures in the diagnosis of reflux disease have been outlined, and the lack of a laboratory test that is both sensitive and specific and suitable for routine clinical use in diagnosing GE reflux has been discussed. Few manometric studies have addressed themselves to the role of the esophagus in the pathogenesis of reflux disease, and the effect of fundoplication on the LES and on the motor function of the body of the esophagus remains controversial.

The objectives of this study have therefore been:

A. To establish the diagnostic value of manometry in GE reflux disease. Resting lower esophageal sphincter pressure, lower esophageal sphincter pressure in response to raised intraabdominal pressure, and distal esophageal pressure changes in response to raised intraabdominal pressure (common cavity test) would all appear to be of potential diagnostic value. This study proposes to evaluate these three tests in combination with the acid infusion test in both normal volunteers and in patients with varying severities of symptomatic GE reflux.

B. To evaluate the motor patterns of the esophagus and LES in symptomatic GE reflux disease, and to examine the effects of fundoplication on these functions.

METHODS

To achieve the aforementioned objectives, two related studies were conducted. In Study A, manometric data from a group of healthy control subjects were compared with data from a group with symptomatic GE reflux disease. The objective of Study A was to determine the value of esophageal manometry in the diagnosis of GE reflux disease. In Study B, manometric data from another group of control subjects were compared with data from a group of patients who underwent studies pre- and postoperatively. The objectives of Study B were to determine the effect of Nissen's fundoplication on the functions of the esophageal body and on the lower esophageal sphincter.

STUDY A

Control Subjects

Forty-one healthy asymptomatic subjects were selected as controls. Of 69 subjects initially interviewed, 28 were excluded from the study on the following grounds: upper gastrointestinal (GI) symptoms in the 2 months before the study or a history of upper GI symptoms that had necessitated antacid therapy or consultation with a physician.

The age range of the control subjects was 18-65 years (mean age 36.6±13.3 yrs) (X±SD).

Patients

Sixty-eight patients with classical symptoms of GE reflux disease were studied. All had been referred to either the gastroenterological

or surgical departments of the University of Alberta Hospital for management of their complaints. They were assigned to the following clinical groups on the basis of the severity of their symptoms:

I. symptoms several times a month and necessitating definite limitations to diet and activity. Otherwise able to function in a normal manner with minor adjustments and intermittent use of therapy (n = 23; mean age = 46.9±9.4 yr).

II. severe symptoms each day unless stringent dietary restrictions taken and strict adherence to therapeutic measures observed (n = 30; mean age = 48.1±9.4 yr).

III. severe symptoms persisting despite stringent dietary restrictions and adequate medical therapy; (n = 15; mean age = 46.6±7.5 yr).

All patients underwent upper GI endoscopy, and were assigned to the following endoscopic groups:

(I) Clinical Esophagitis: Classical symptoms of GE reflux and normal upper GI endoscopy (n=24; mean age = 48.2±9.6 yr).

(II) Esophagitis: Classical symptoms of GE reflux and erythema in the distal esophagus. (n=25; mean age = 47.5±7.6 yr).

(III) Erosive esophagitis: Classical symptoms of GE reflux, with erythema, erosions, and/or ulceration in the distal esophagus.

STUDY B

Control subjects:

Eighteen asymptomatic subjects were selected as controls. Criteria for inclusion were the same as those for Study A. The age range of this group was from 18 years to 62 years (mean age, 33.1±15.9 yr).

Patients

Thirty-two patients were studied. All had severe persistent symptoms of GE reflux disease despite adequate medical therapy. All had undergone radiological, endoscopic, and manometric examinations. Hiatus hernia was present in 23/32 (72%). Endoscopic esophagitis was present in 17/32 (53%), and 2 of these (6%) had ulceration of the esophagus. A summary of the clinical, radiologic and endoscopic findings is given in Table 1.

All patients underwent a modified Nissen fundoplication (90% peri-esophageal wrap), resulting in good to excellent relief of symptoms in all. Esophageal manometry was repeated in all patients within 3-11 months (mean, 6 months) post-operatively.

The age range of the patient group was 24 years to 69 years (mean age 46.2±12.6 yr).

TABLE 1.

Summary of the clinical, endoscopic and radiologic findings in 32 patients with symptomatic GE reflux.

Sex ratio. M : F	2 : 1
Mean age	46.2 ± 12.6yr
Duration of Symptoms	10.0 ± 8.3yr
Heartburn	87%
Regurgitation	68%
High epigastric pain	63%
Chest pain	23%
Dysphagia	23%
Esophagitis	53%
Hiatus hernia	72%

Esophageal manometry

The manometric study performed in both study groups was identical.

A catheter assembly consisting of 6 fused polyethylene tubes was used (ID 1.19 mm., OD 1.70 mm). Each catheter had a lateral opening equal to the I.D. of the tube itself, and was closed distal to this opening. The openings on tubes, numbers 1-5 (Fig. 2a) were at 5 cm intervals, except opening numbers 2 and 3, which were placed 1 cm apart. The orad three openings were orientated circumferentially to lie at 120 degrees to each other (Fig. 2b). Tube number 6 was used for the acid infusion test[11].

Subjects and patients were instructed to fast for at least 12 hours, prior to the study.

The catheter assembly was introduced orally, without prior sedation or anesthesia, into the stomach. Tubes number 1-4 were filled with water and perfused at a constant rate of 0.3 ml/min, using an Arndorfer pump.

The water-filled catheters were used to transmit intraluminal pressure to external Statham pressure transducers. The output from each transducer was recorded on a Honeywell light-pen recorder, model no. 1508A. The recording system was calibrated in cm H_2O before the start of each study.

Resting Lower Esophageal Sphincter Pressure (R.LESP):

The tube assembly was withdrawn at 0.5 cm intervals until the orad three openings traversed the sphincteric zone and entered the esophagus. The subject was instructed not to swallow during this part of the test. After each withdrawal, the assembly was left in position

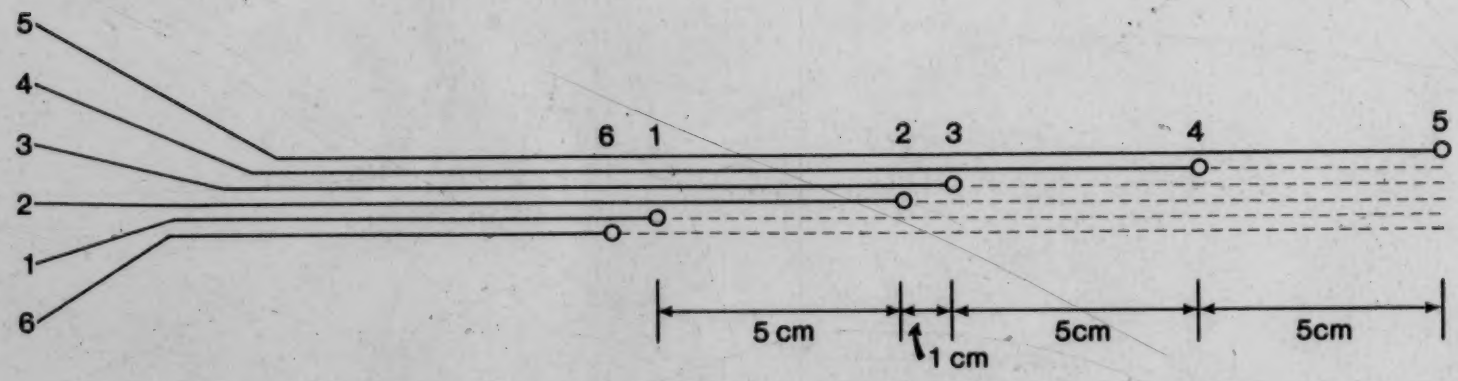
FIGURE 2A

Schematic representation of open tipped catheter assembly

FIGURE 2B

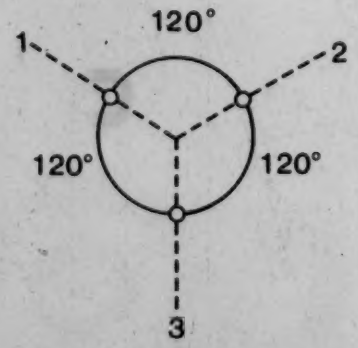
Circumferential placement of catheter openings between catheters nos. 1, 2, and 3

(a)



Schematic representation of open tipped catheter assembly.

(b)



Circumferential placement of catheter openings between catheters nos. 1, 2, and 3.

stationary pull-through measurements of R.LESP were obtained.

Response of the LES to abdominal compression (C.LESP)

The assembly was re-inserted into the stomach and intra-abdominal pressure was raised by inflating a large pressure cuff, placed around the upper abdomen, to a pressure of 50 mm.Hg. With abdominal compression maintained, a stationary pull-through measurement of LES pressure was repeated.

Commmon Cavity Test (CCT):

Tube no. 5 was now connected to the pressure transducers in place of tube no. 2. Thus, the distal openings of the tube was in the following positions: no. 1 and 3, in the esophagus, 10 cm and 5 cm proximal to the LES; no. 4 in the sphincter zone; and no. 5 in the stomach, 5 cm distal to the LES. A baseline recording was obtained from these levels, then abdominal compression (50 mmHg) was applied for 30 sec. When the compression was released, and baseline readings stabilized, 80 mmHg compression was applied to the abdomen for 30 sec. The subject was given 300 ml of water to drink, and the test was repeated at both levels of abdominal compression for 30 sec each time.

Deglutition study

With tube no. 2 reconnected to the transducers in place of no. 5, the catheter assembly was again inserted into the stomach and was positioned so that the proximal opening was in the sphincter zone. The response of the LES to wet swallows (5 ml H_2O bolus per swallow) was recorded, the assembly being withdrawn 0.5 cm after each swallow until

all tube openings were in the esophagus.

Esophageal peristalsis

With all four functioning tubes in the body of the esophagus, esophageal peristaltic activity in the upper, middle and lower esophagus in response to 10 consecutive wet swallows was recorded.

Acid infusion test (AIT)

Finally, water was infused for 3 min through tube no. 6. The subject was instructed to inform the examiner of any discomfort or clear-cut symptoms referable to the retrosternal, pharyngeal, or epigastric regions. Subjects were requested to describe any symptoms experienced, to indicate the exact moment of onset, indicate whether any such symptoms improved or disimproved, and indicate the exact moment that any such symptoms disappeared. After 3 min of water infusion, 0.IN hydrochloric acid was infused at 8 ml/min. Subjects were not told when and whether acid was being infused. The time of onset and nature of any symptoms developed were noted. If significant symptoms (e.g., heartburn) developed, the infusion was switched to water and the disappearance of symptoms was noted. If no significant symptoms developed by 20 min of acid infusion, the test was discontinued.

The catheter assembly was withdrawn and the subject was allowed to resume normal activity. The manometric examination of the esophagus thus described takes between 1 1/2 and 2 hours to perform and is well tolerated by most subjects.

Analysis of Records - Study A

All records in this study were read blindly, without knowledge of whether the record being evaluated belonged to a control subject or a patient. Further, all indices were read separately and independently of one another.

Resting Lower Esophageal Sphincter Pressure

R.LESP was determined from the end-expiratory gastric pressure (referred to as zero) and end-expiratory sphincter pressure. R.LESP values were expressed as the mean of the pressures recorded from the pull-through of the three orad catheter openings.

Response of the LES to compression

C.LESP was determined in the same manner as R.LESP, and changes in gastric pressure (ΔG) and in sphincter pressure (ΔS) in response to compression were measured. Thus, the ratio $\Delta S/\Delta G$ could be calculated.

Common Cavity Test

The CCT was interpreted qualitatively, being designated negative (-), equivocal (?), significant rise in intra-esophageal pressure (+), or a rise in intra-esophageal pressure to the level of intragastric pressure (++). As evidence of reflux, these were interpreted respectively as denoting no reflux, equivocal evidence, moderate reflux and marked reflux.

Acid-infusion Test

If the infusion of acid gave rise to no symptoms or vague symptoms unrelated to reflux disease occurred, or vague symptoms occurred whether the infusate was water or acid, the test was regarded as negative. If epigastric or retrosternal pain or burning occurred in either the controls or the patients when acid was infused and cleared when water was substituted, the test was regarded as positive. In the patients, if symptoms identical to those experienced at home occurred when acid was infused and cleared when water was substituted, the test was also regarded as positive.

Sensitivity and Specificity

For a diagnostic test to be useful, it must be both sensitive ([diseased patients with positive test/diseased patients] x 100%) and specific ([non-diseased subjects with negative test/non-diseased subjects] x 100%) for the abnormality tested. Of the four tests considered (R.LESP, C.LESP, CCt, AIT), each individual test and a variety of test combinations were evaluated for sensitivity and specificity in diagnosing GE reflux disease.

Analysis of Records - Study B

R.LESP; C.LESP; $\Delta S/\Delta G$

These variables were calculated and expressed in the same manner as for Study A.

Response of the LES to deglutition (Fig. 3)

a. LES relaxation. The amplitude and duration of relaxation of the LES in response to wet swallows was measured. Any residual gradient between the final LES relaxation pressure and resting gastric pressure was measured.

b. Post-deglutitive LES contraction. The amplitude and duration of the post-deglutitive LES contraction was measured.

Esophageal Peristaltic Activity (Fig. 4)

The amplitude and duration of 10 consecutive peristaltic contractions were measured in the upper, middle, and lower esophagus. Values from each subject were expressed as the mean of 10 values obtained at each site. The incidence of aperistaltic contractions was noted.

Statistical Methods

All values in both studies were expressed as the mean ± one standard deviation of the mean.

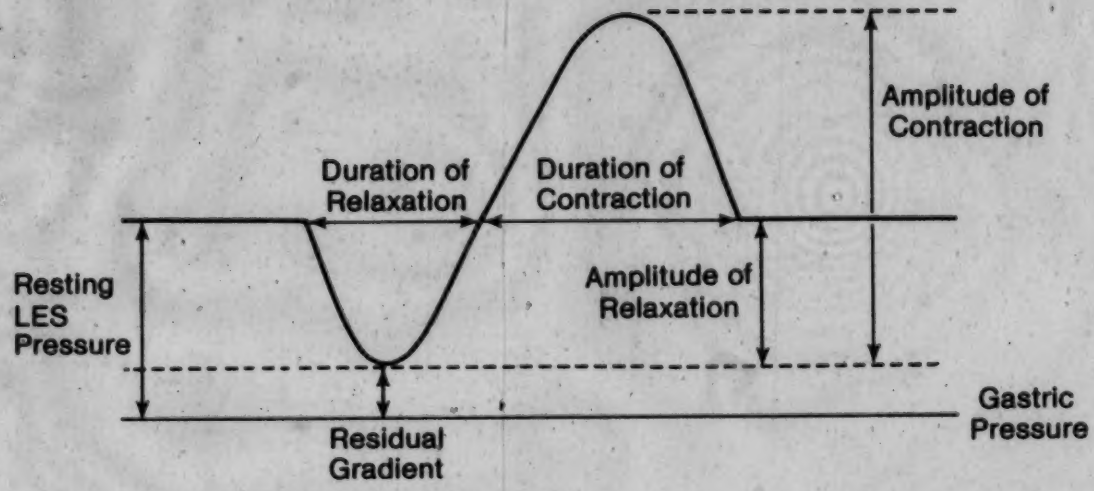
Significance levels for the difference between groups were calculated with the unpaired Student's *t* test or (for pre- and postoperative data in Study B) paired *t* test.

In Study A, four diagnostic indices per subject were considered; i.e., R.LESP, C.LESP, CCT, and AIT. Each test was designated a positive, equivocal, or negative index of of GE reflux disease.

Based upon the number of positive, equivocal, or negative test

FIGURE 3

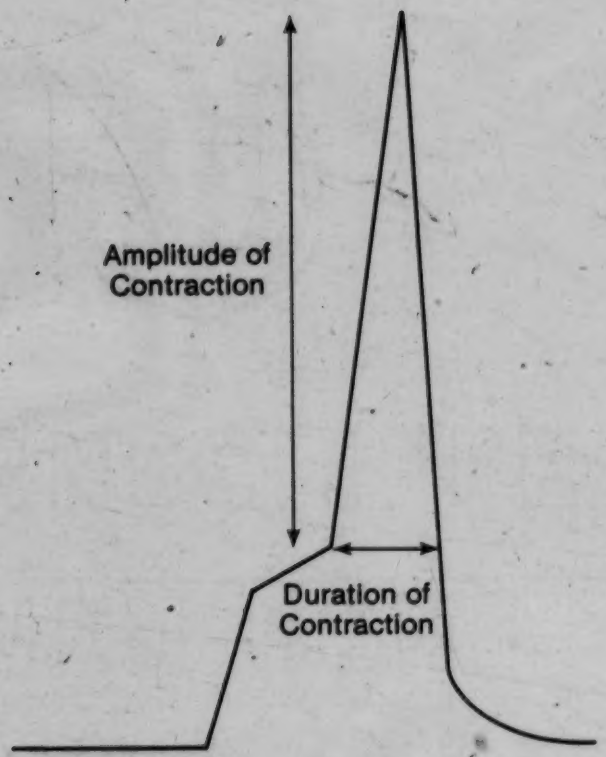
Response of the LES to deglutition



Diagrammatic representation of response of lower esophageal sphincter to deglutition.

FIGURE 4

Diagrammatic representation of esophageal peristaltic contraction



Diagrammatic representation of esophageal peristaltic contraction.

results in any one individual, the probability of such an individual having GE reflux disease was calculated. The theoretical basis for this analysis of probability is detailed in the Appendix 1.

RESULTS

Study A

Resting Lower Esophageal Sphincter Pressure (Table 2,3,4; Fig.5)

The patient group had a R.LESP in the range of 0-29 cm H_2O (mean 7.0±6.2 cm H_2O) which was significantly lower ($P<0.001$) than that observed in the control group (range 4-41 cm H_2O; mean 14.7±5.8 cm H_2O). The lowest R.LESP measurements were seen in the erosive esophagitis group (range 0-12 cm H_2O; mean 4.5±3.6 cm H_2O). Only one control subject had a R.LESP value less than 8 cm H_2O, while 44 patients had a value below this level. There was considerable overlap between individual sphincter pressure measurements in the control and patient groups in the range of 8 to 20 cm H_2O; two patients had R.LESP measurements greater than 20 cm H_2O. This overlap was least marked between controls and the erosive esophagitis group; no patients in this group having a R.LESP measurement greater than 12 cm H_2O, and only 4/19 of them having a value greater than 8 cm H_2O. R.LESP measurements were significantly lower ($P<0.025$) in the erosive esophagitis group than in the clinical esophagitis group (range 0-29 cm H_2O; mean 9.6±7.6 cm H_2O), but were not significantly different ($P>0.05$) between the other group combinations. Thus, while there was a correlation between poor resting LES pressures and the degree of endoscopic esophagitis, R.LESP did not correlate with the severity of presenting symptoms.

TABLE 2.

Mean lower esophageal sphincter pressures at rest in control subjects and patient groups in cm H_2O.

Controls (n=41)	14.7 ± 5.8
Symptomatic groups	
I (n=23)	6.7 ± 6.8
II (n=30)	6.8 ± 5.5
III (n=15)	7.2 ± 6.5
Endoscopic groups	
Clinical esophagitis (n=24)	9.6 ± 7,6
Esophagitis (n=25)	6,1 ± 5,2
Erosive esophagitis (n=19)	4.5 ± 3.6
All patients (n=68)	7.0 ± 6.2

Table 3

Resting lower esophageal sphincter pressures in control subjects and endoscopic groups, expressed as percentages

	<4 cm H_2O	4–7 cm H_2O	8–12 cm H_2O	>12 cm H_2O
Controls (n=41)	0	2	32	66
Clinical Esophagitis (n=24)	21	29	17	33
Esophagitis (n=25)	28	48	8	16
Erosive Esophagitis (n=19)	36	24	16	0
All Patients (n=68)	31	37	15	17

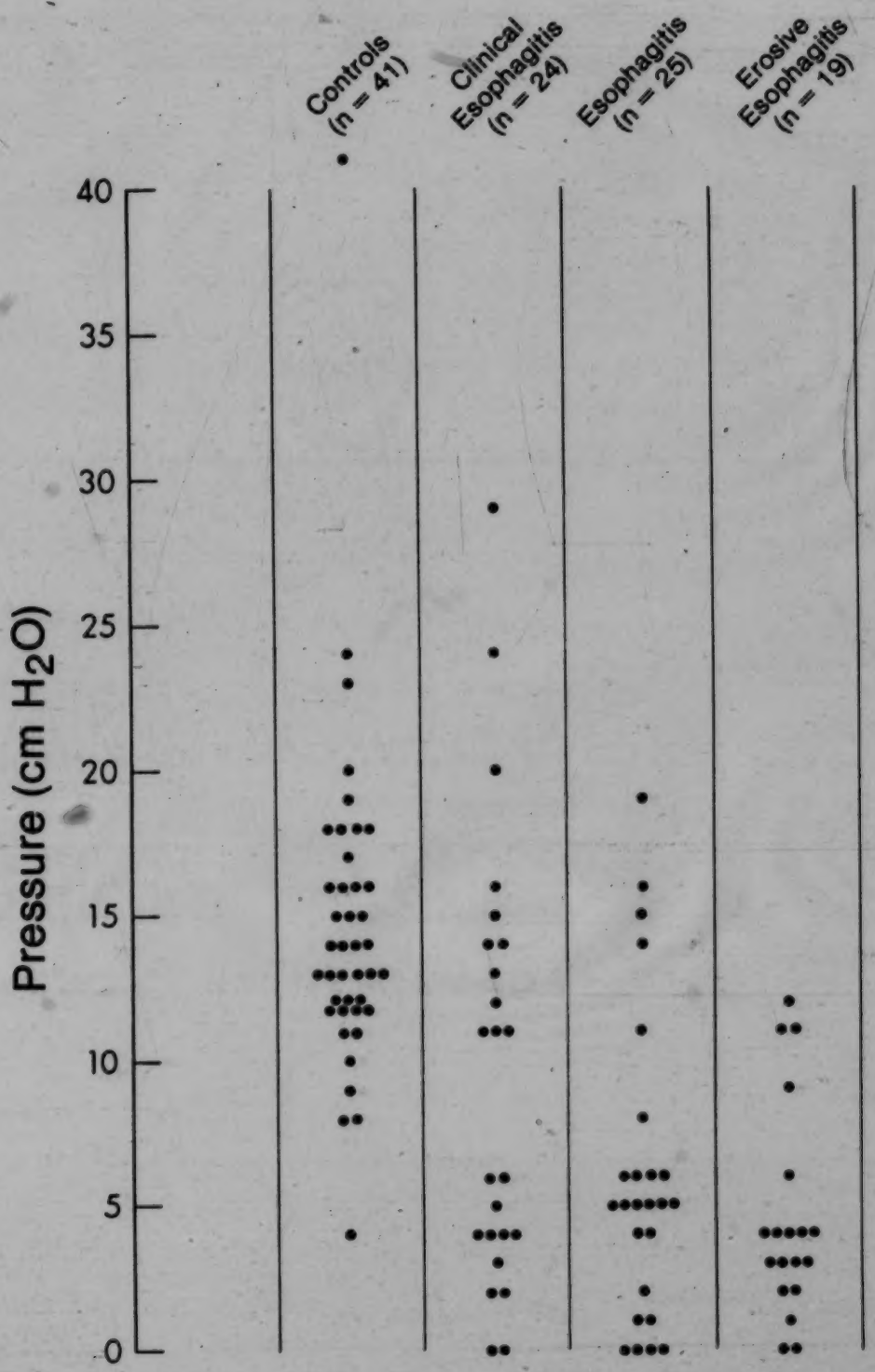
TABLE 4.

Resting lower esophageal sphincter pressures in control subjects and symptomatic groups, expressed as percentages.

	<4cmH_2O	4-7cmH_2O	8-12cmH_2O	>12cmH_2O
Controls (n=41)	0	2	32	66
Grade I (n=23)	35	35	22	8
Grade II (n=30)	33	33	11	23
Grade III (n=15)	20	47	13	20
All patients (n=68)	31	37	15	17

FIGURE 5

Lower esophageal sphincter pressures at rest
in control subjects and patient groups



Lower esophageal sphincter pressures at rest in control subjects and patient groups.

Response of the LES to Abdominal Compression (Table 5,6,7, Fig. 6)

The LES response to abdominal compression was poor in the patient group (range 0-16 cm H_2O; mean 4.1±4.7 cm H_2O) and was significantly lower $P<0.001$ than the C.LESP observed in the control group (range 3-34 cm H_2O; mean 16.6±6.6 cm H_2O). The lowest C.LESP measurements were seen in the erosive esophagitis group (range 0-16 cm H_2O; mean 2.4±4.0 cm H_2O). Two control subjects had C.LESP values less than 8 cm H_2O, while 55/68 patients had a C.LESP value below this level. Thirty-six control subjects and only 7/68 patients had a C.LESP value above 12 cm H_2O, thus the overlap between patients and controls was much less marked than that observed with R.LESP measurements. In the erosive esophagitis group, the sphincter was abolished in response to compression in 11/19 patients, and was less than 8 cm H_2O in 18/19 patients. In the esophagitis group, the sphincter was abolished in response to compression in 11/25 patients, and was less than 8 cm H_2O in 21/35 patients. Somewhat better responses to compression were seen in the clinical esophagitis group, the sphincter being abolished in 3/24 patients, although the overall mean in this group (5.5±4.5 cm H_2O) was still significantly lower ($P<0.001$) than that of the control group. C.LESP measurements were significantly lower ($P<0.025$) in the erosive esophagitis group than in the clinical esophagitis group but were not significantly different ($P>0.1$) between the other group combinations. C.LESP measurements showed a correlation with the endoscopic severity of disease, but did not not correlate with symptomatic severity.

ΔS/ΔG (Table 8)

In 30/41 control subjects, ΔS/ΔG ratio was greater than 1.00; three

TABLE 5.

Mean lower esophageal sphincter pressures in response to compression in control subjects and patient groups, in cm H_2O.

Controls (n=41)	16.6 ± 6.6
Symptomatic groups	
I (n=23)	3.9 ± 4.7
II (n=30)	4.1 ± 4.3
III (n=15)	3.6 ± 4.7
Endoscopic groups	
Clinical esophagitis (n=24)	5.5 ± 4.5
Esophagitis (n=25)	3.6 ± 4.5
Erosive esophagitis (n=19)	2.4 ± 4.0
All patients (n=68)	4.1 ± 4.7

Table 6

Lower esophageal sphincter pressures in response to abdominal compression in control subjects and patient groups, expressed as percentages

	<4 cm H_2O	4-7 cm H_2O	8-12 cm H_2O	>12 cm H_2O
Controls (n=41)	2	2	18	78
Clinical Esophagitis (n=24)	46	21	25	8
Esophagitis (n=25)	60	24	8	8
Erosive Esophagitis (n=19)	74	21	0	5
All patients (n=68)	59	22	12	7

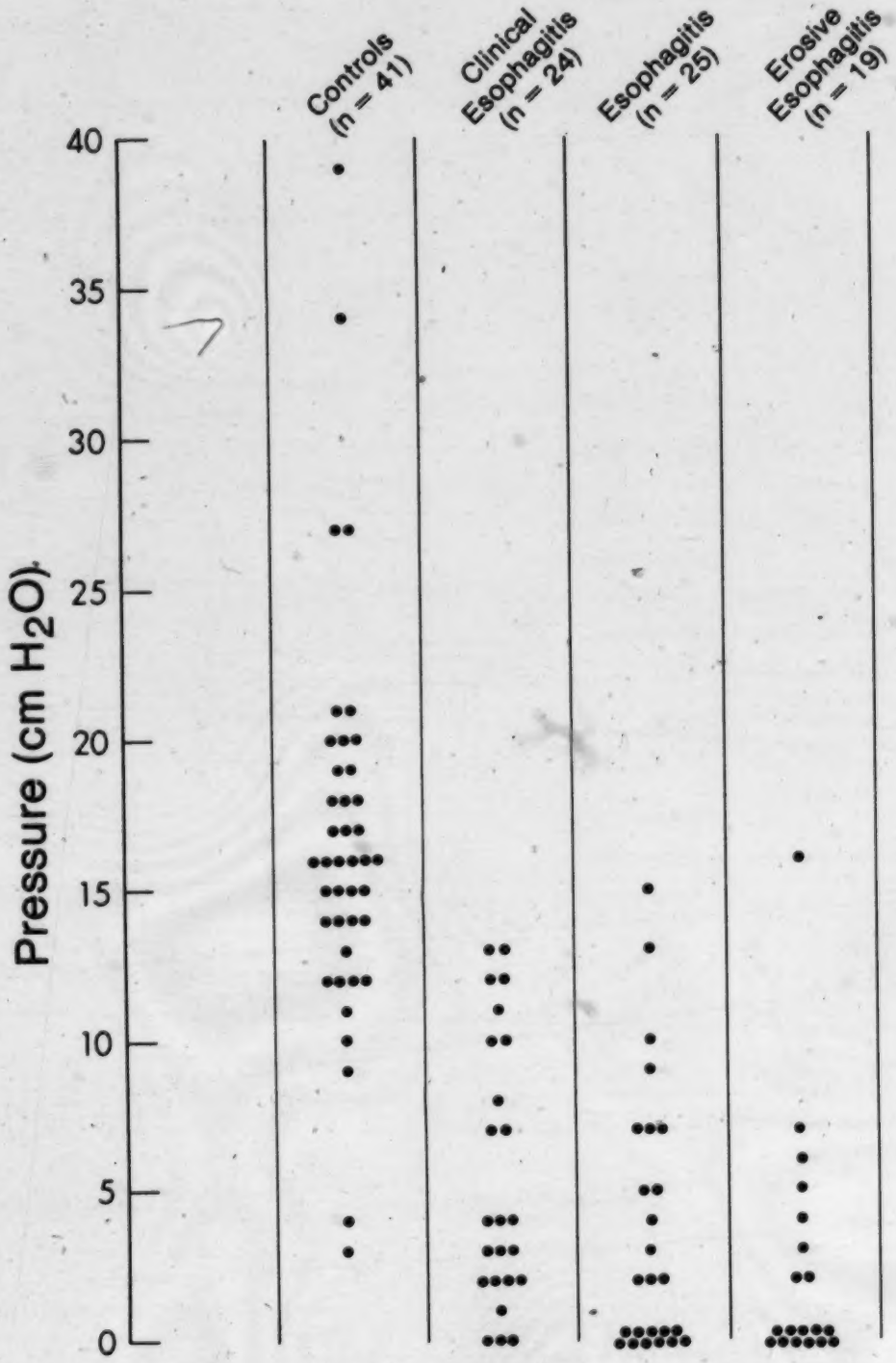
TABLE 7.

Lower esophageal sphincter pressures in response to abdominal compression in control subjects and symptomatic groups, expressed as percentages.

	$< 4cmH_2O$	$4-7cmH_2O$	$8-12cmH_2O$	$> 12cmH_2O$
Controls (n=41)	2	2	18	78
Grade I (n=23)	61	17	13	19
Grade II (n=30)	53	30	10	7
Grade III (n=15)	67	13	13	1
All patients (n=68)	59	22	12	7

FIGURE 6

Lower esophageal sphincter pressures in response to abdominal compression in control subjects and patients



Lower esophageal sphincter pressures in response to abdominal compression in control subjects and patients.

subjects had values of 1.00, and eight subjects had values less than 1.00. In the patient group 49/68 had values less than 1.00, five had values equal to 1.00, and 14 had values greater than one. The mean patient value (0.77±0.37) was significantly lower ($P<0.001$) than the mean value of the control subjects (1.12±0.23).

Table 8

$\Delta S/\Delta G$ Ratios in control subjects and patient groups, expressed as percentages.

	<1	=1	>1
Controls (n=41	20	7	73
Clinical Esophagitis (n=24)	75	4	21
Esophagitis (n=25)	68	8	24
Erosive Esophagitis (n=19)	74	10	16
All patients	72	7	21

Common Cavity Test (Table 9,10)

The common cavity test showed a significant rise in intraesophageal pressure in 7/41 controls. A marked rise (equating with intragastric pressure) was not observed among the control group. A total of 53/68 patients had significantly positive results, 37 of these showing marked elevations in distal esophageal pressure. Seven patients had equivocal results and eight had negative results.

In the erosive esophagitis group, 18/19 patients had significant results, 12 of these being marked. In the esophagitis group, 20/25 patients had significant results, 15 of these being marked. Three patients in this group had a negative result. In the clinical esophagitis group, 15/24 had a significant result, 10 of these showing evidence of marked reflux. Five of these patients had a negative result.

Acid Infusion Test (Table 11,12)

In the control group, 33/41 subjects had a negative result. Of the eight positive results, four occurred within five minutes of acid infusion. Among the patients 13/68 had a negative result. Of 55/68 positive results, 47 occurred within 5 minutes, and 36 within two minutes of acid infusion. The highest incidence of negative results was observed in the erosive esophagitis group, and the lowest incidence of negative resutls was observed in symptomatic group III.

Table 9.

Qualitative results of the common cavity test in control subjects and endoscopic groups, expressed as percentages

	++	+	?	-
Controls (n=41)	0	17	12	71
Clinical Esophagitis (n=24)	42	21	16	21
Esophagitis (n=25)	60	20	8	12
Erosive Esophagitis (n=19)	63	32	5	0
All patients (n=68)	54	24	10	12

TABLE 10.

Qualitative results of the common cavity test in control subjects and symptomatic groups, expressed as percentages.

	++	+	?	-
Controls (n=41)	0	17	12	71
Grade I (n=23)	52	26	22	0
Grade II (n=30)	53	23	17	7
Grade III (n=15)	60	20	13	7
All patients (n=68)	54	24	10	12

Table 11

Results of acid infusion test in control subjects and endoscopic groups, expressed as percentages

	Positive < 2 min	Positive 3-5 min	Positive 6-10 min	>10 or Negative
Controls (n=41)	2	7	10	81
Clinical Esophagitis (n=41)	54	17	17	12
Esophagitis (n=25)	52	24	12	12
Erosive Esophagitis (n=19)	53	5	5	37
All Patients (n=68)	53	16	12	19

TABLE 12

Results of acid infusion test in control subjects and symptomatic groups, expressed as percentages.

	<2min	3-5min	6-10min	>10min or neg.
Controls (n=41)	2	7	10	81
Grade I (n=23)	57	9	13	21
Grade II (n=30)	47	20	13	20
Grade III (n=15)	60	20	13	7
All patients (n=68)	53	16	12	19

Evaluation of individual tests (Tables 13, 14)

For purposes of evaluation, each test was designated as being marked positive, equivocal or negative as a diagnostic index of GE reflux disease. Table 13 gives the range of values assigned to each test.

Table 14 gives the sensitivity and specificity for each individual test.

While low R.LESP values were highly specific, this test alone had poor sensitivity in detecting reflux disease. A value below 4 cm H_2O was not observed in controls, and may be considered diagnostic of the condition.

A C.LESP value below 8 cm H_2O, while having a similar specificity, is a more sensitive test for reflux disease than R.LESP measurements.

The common cavity test detected almost 80% of reflux patients, but had a high false positive rate (17%) among controls. However, a marked positive result was diagnostic of reflux disease.

An acid infusion test positive in less than 5 minutes had good specificity (91%) for GE reflux disease, and a sensitivity approaching 70%.

TABLE 13.

Designation of test results.

++	Marked positive
+	Positive
?	Equivocal
-	Negative

	++	+	?	-
R.LESP ($cm\ H_2O$)	< 4	4-7	8-12	> 12
C.LESP ($cm\ H_2O$)	< 4	4-7	8-12	> 12
CCT	++	+	?	-
AIT (mins)	< 2	3-5	6-10	> 10

TABLE 14

Evaluation of diagnostic value of four individual tests.

		Sensitivity.	Specificity.
R.LESP.	+	68%	98%
	++	31%	100%
C.LESP.	+	81%	96%
	++	59%	98%
CCT.	+	78%	83%
	++	54%	100%
AIT.	+	69%	91%
	++	53%	98%

Evaluation of test combinations (Table 15, 16)

Tables 15 and 16 give the distribution of positive test responses in control subjects, and in symptomatic and endoscopic patient groups. If any two tests were positive, this combination showed a sensitivity of 93% and a specificity of 95%. Three or more positive tests had a sensitivity of 70% and specificity of 100%.

Assuming, therefore, that any two or more positive test responses be the criteria for diagnosing GE reflux disease, these test combinations show a sensitivity of between 92% and 94% among the symptomatic groups. Among the endoscopic groups, all patients with endoscopic esophagitis were identified. The test combinations showed poorest sensivivity (79%) among the endoscopically normal group (clinical esophagitis), 2/24 of these patients having no positive test.

A total of 22/68 patients had resting LES pressures in the equivocal or negative range. Of 10/22 with equivocal results, all had two or more of the other tests positive. Of 12 patients with negative R.LESP results, eight had two or more tests positive. Thus, 82% of patients with negative or equivocal results on testing resting LES pressure were identified by this test combination.

All but one patient with a marked positive result on R.LESP testing, and all patients with a marked positive common cavity test had at least one positive response to the other tests.

All patients with either a positive or a marked positive response to C.LESP testing had at least one other positive response to the other tests. All but two patients with either a positive or marked positive response to acid infusion testing had at least one other positive response to the other tests.

TABLE 15.

No. of positive responses to four tests in control subjects and symptomatic groups, expressed as percentages.

	0	1	2	3	4
Controls (n=41)	71	24	5	0	0
Grade I (n=23)	4	4	17	44	31
Grade II (n=30)	3	3	27	30	37
Grade III (n=15)	0	7	20	33	40
All patients (n=68)	3	4	23	35	35

Table 16

No. of positive responses to four tests in control subjects and endoscopic groups, expressed as percentages

	0	1	2	3	4
Controls (n=41)	71	24	5	0	0
Clinical Esophagitis (n=24)	8	13	29	21	29
Esophagitis (n=25)	0	0	28	28	44
Erosive Esophagitis (n=19)	0	0	5	63	32
All patients (n=68)	3	4	23	35	35

Probablities of having G.E. reflux (Table 17)

To extrapolate data from this sample to the general population, the distribution of the number of positive test responses in the control subjects and the patients closely fitted the Poisson distribution (Appendix I). Thus, we can calculate the probablility that an individual selected at random, who exhibits a certain number of positive test responses, has GE reflux disease. The reported incidence of GE reflux disease is between 7% and 36%[215], and table 17 gives the probabilities of having GE reflux, given X number of positive tests, for a range of incidences from 1% to 40%.

Thus, we may draw the following conclusions: any individual exhibiting three or more positive responses to these tests almost certainly has GE reflux disease; any individual exhibiting a R.LESP below 4 cm H_2O, or a markedly positive common cavity test, almost certainly has GE reflux disease; any individual exhibiting at least two positive test responses has a high probability of having GE reflux disease; any individual showing a poor sphincter response to abdominal compression has a high probability of having the disease; a positive common cavity test alone or an early positive acid infusion test alone is not sufficient to establish a diagnosis of GE reflux.

TABLE 17.

Probability table of a randomly selected individual having GE reflux disease, given that he exhibits X no. of positive responses to four tests, for a population incidence range from 1% to 40%.

Pr(P) = incidence in population,
X = 0, 1+, 2+, 3+, or 4 pos. tests.

X	0	1+	2+	3+	4
Pr(P)					
.01	.00	.03	.16	.59	.89
.05	.00	.15	.50	.88	.98
.10	.00	.27	.69	.94	.99
.15	.00	.37	.78	.96	.99
.20	.00	.46	.83	.97	.99
.25	.01	.53	.88	.98	.99
.30	.01	.59	.89	.98	.99
.35	.01	.65	.91	.99	.99
.40	.02	.69	.93	.99	.99

Study B

Resting Lower Esophogeal Sphincter Pressure (Table 18, Fig. 7)

The pre-operative patient group had an R.LESP in the range of 0.0 to 19.0 cm H_2 (8.0±5.5 cm H_2O), significantly lower ($P<0.001$) than that observed in the control group (range 11 to 20 cm H_2O; mean 14.5±3.0 cm H_2O). Post-operatively, these same patients had an R.LESP in the range of 0.0 to 25.0 cm H_2O (mean 14.5±6.0 cm H_2O) which was significantly higher than they had pre-operatively, ($P<0.001$) but not significantly different from the control group.

Response of the LES to Abdominal Compression (Table 18, Fig. 8)

The LES response to compression was poor in the pre-operative group (range 0.0 to 16.0 cm H_2O; mean 5.0±5.0 cm H_2O), and was significantly lower ($P<0.001$) than the C.LESP observed in the control group (range 11 to 5 cm H_2O; mean 18.5±3.5 cm H_2O). The patients had a significantly higher C.LESP post-operatively (range 0 to 26 cm H_2O; mean 13.5±6.5 cm H_2O; $P<0.001$) but which was still significantly lower ($P<0.025$) than that observed in the control group.

$\Delta S/\Delta G$ (Table 19)

In 16/18 control subjects, $\Delta S/\Delta G$ ratio was greater than 1.00; one subject had a value of 1.00, and one a value less then 1.00. Pre-operatively, all but 3/32 patients had a $\Delta S/\Delta G$ ratio less than 1.00, the mean being significantly lower ($P<0.001$) than the mean value of the control subjects. Post-operatively, 13/32 patients had a value greater

TABLE 18.

Lower esophageal sphincter pressures at rest and in response to abdominal compression in control subjects and pre- and post-operative patient groups, in cm H_2O.

	R.LESP.	C.LESP.	ΔS/ΔG.
Controls (n=18)	14.5±3.0	18.5±3.5	1.3±0.3
Pre-op. (n=32)	8.0±5.5	4.5±5.0	0.8±0.3
Post-op. (n=32)	14.5±6.0	13.5±6.5	1.0±0.3

Statistical analysis

	R.LESP.	C.LESP.	ΔS/ΔG.
C. vs Pre-op.	$P < 0.001$	$P < 0.001$	$P < 0.001$
Pre. vs Post.	$P < 0.001$	$P < 0.001$	$P > 0.05$
C. vs Post-op.	$P > 0.5$	$P < 0.025$	$P < 0.01$

TABLE 19

$\Delta S/\Delta G$ Values in control subjects, and in patients both pre- and post-operatively, expressed as percentages

	<1	=1	>1
Controls (n=18)	5	5	90
Pre-op. (n=32)	75	16	9
Post-op (n=32)	56	6	38

than 1.00, not significantly higher than the mean pre-operative value but significantly lower ($P<0.01$) than the mean control value.

Response of the LES to Deglutition (Table 20)

In all control subjects, LES relaxation in response to deglutition was complete, R.LESP falling to the level of intragastric pressure. Pre-operatively, only 2 patients had incomplete LES relaxation, a residual stomach sphincter gradient of 4 cm H_2O being recorded in both. Post-operatively, 2 patients showed complete failure of the LES to relax during deglutition; 5 patients had complete LES relaxation; in 2 patients, the LESP was too feeble for discernment of relaxation; and in 24 patients, LES relaxation was incomplete, leaving a mean residual stomach sphincter gradient of 4.0±4.0 cm H_2O in the post-operative group.

The duration of LES relaxation in response to deglutition was not significantly different between the groups.

The mean amplitude of the post-deglutitive LES contraction was significantly lower ($P<0.05$) in the pre-operative patients than in either the control or post-operative group. The mean duration of this contraction was also significantly lower ($P<0.025$) in the pre-operative group than in the other groups.

Esophageal Peristaltic Activity (Tables 21 and 22, Fig.9)

The mean amplitudes of esophageal peristaltic contractions observed at all recording sites were significantly lower ($P<0.001$) among the pre-operative patients than in the other groups. Post-operatively, the mean

Table 20

RESPONSE OF LES TO DEGLUTITION

DEGLUTITION	Amplitude of relaxation (cms. H_2O)	Duration of relaxation (seconds)	Residual (cms. H_2O)	Amplitude of contraction cms. H_2O)	Duration of contraction (seconds)
Controls	14.0±2.5	11.0±3.0	0.0±0.0	22.5±4.0	15.5±3.5
Pre-op	7.0±5.5	8.0±5.0	0.5±1.0	15.5±11.5	13.0±5.0
Post-op	10.0±5.0	10.0±5.0	4.0±4.0	21.5±12.5	17.0±7.5

STATISTICAL ANALYSIS	Amplitude of relaxation P	Duration of relaxation P	Residual P	Amplitude of contraction P	Duration of contraction P
C. vs Pre-op	<0.001	NS	NS	<0.05	NS
Pre vs Post	<0.005	NS	<0.001	<0.05	<0.025
C. vs Post-op	<0.025	NS	<0.005	NS	NS

Table 21

AMPLITUDE OF ESOPHAGEAL CONTRACTIONS: (cm of H_2O)

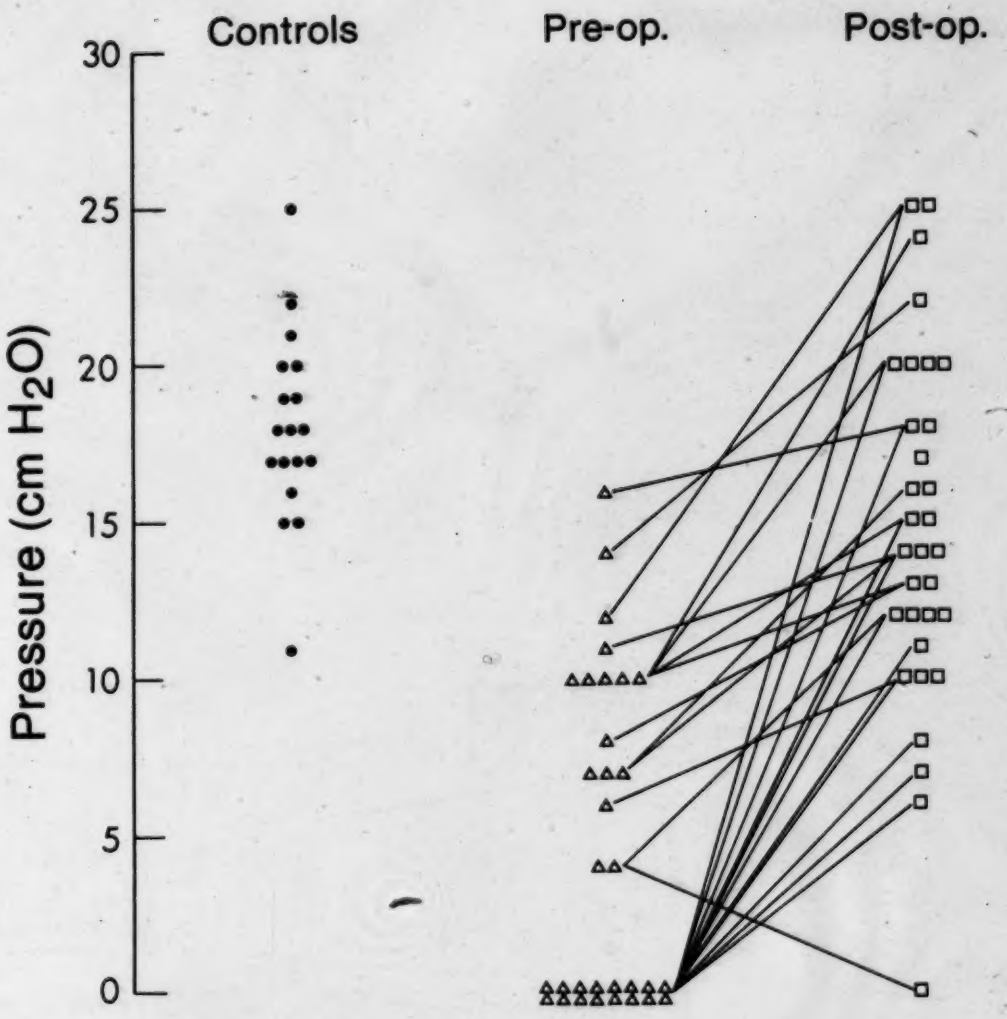
	Upper	Middle	Lower
Controls	62 ± 4	76 ± 7	94 ± 6
Pre-op	45 ± 14	51 ± 21	61 ± 29
Post-op	64 ± 26	82 ± 39	103 ± 50

STATISTICAL ANALYSIS

	Upper P	Middle P	Lower P
C vs Pre-op.	<0.025	<0.001	<0.001
Pre. vs Post.	<0.001	<0.001	<0.001
C vs Post-op.	NS	NS	NS

FIGURE 7

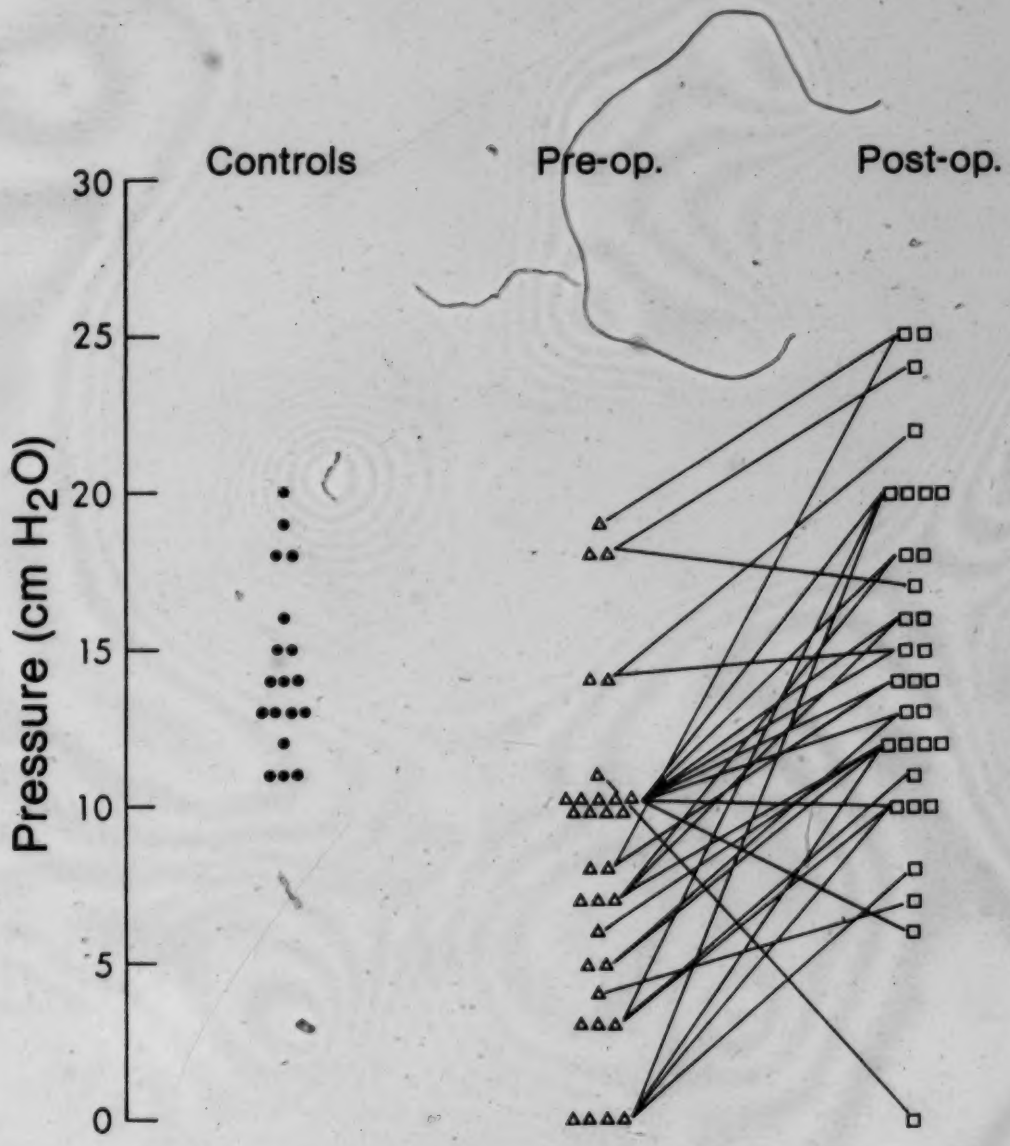
Lower esophageal sphincter pressure at rest in 18 control subjects (●) and 32 patients both pre-(Δ) and post-operatively(■)



Lower esophageal sphincter pressure in response to abdominal compression in 18 control subjects (•) and 32 patients both pre-(△) and post-operatively (□).

FIGURE 8

Lower esophageal sphincter pressure in response to abdominal compression in 18 control subjects (●) and 32 patients both pre-(Δ) and post-operatively(□).



Lower esophageal sphincter pressure at rest in 18 control subjects (•) and 32 patients both pre-(△) and post-operatively(□).

Table 22

DURATIONS OF ESOPHAGEAL CONTRACTIONS: (Seconds)

	Upper	Middle	Lower
Normals	4.5 ± 0.5	5.0 ± 0.5	5.5 ± 0.5
Pre-op.	3.5 ± 0.5	4.0 ± 1.0	4.0 ± 1.0
Post-op.	4.5 ± 1.0	5.0 ± 1.5	6.0 ± 1.5

STATISTICAL ANALYSIS

	Upper P	Middle P	Lower P
N. vs Pre-op	<0.005	<0.005	<0.005
Pre. vs Post.	<0.001	<0.001	<0.001
N. vs Post-op.	NS	NS	NS

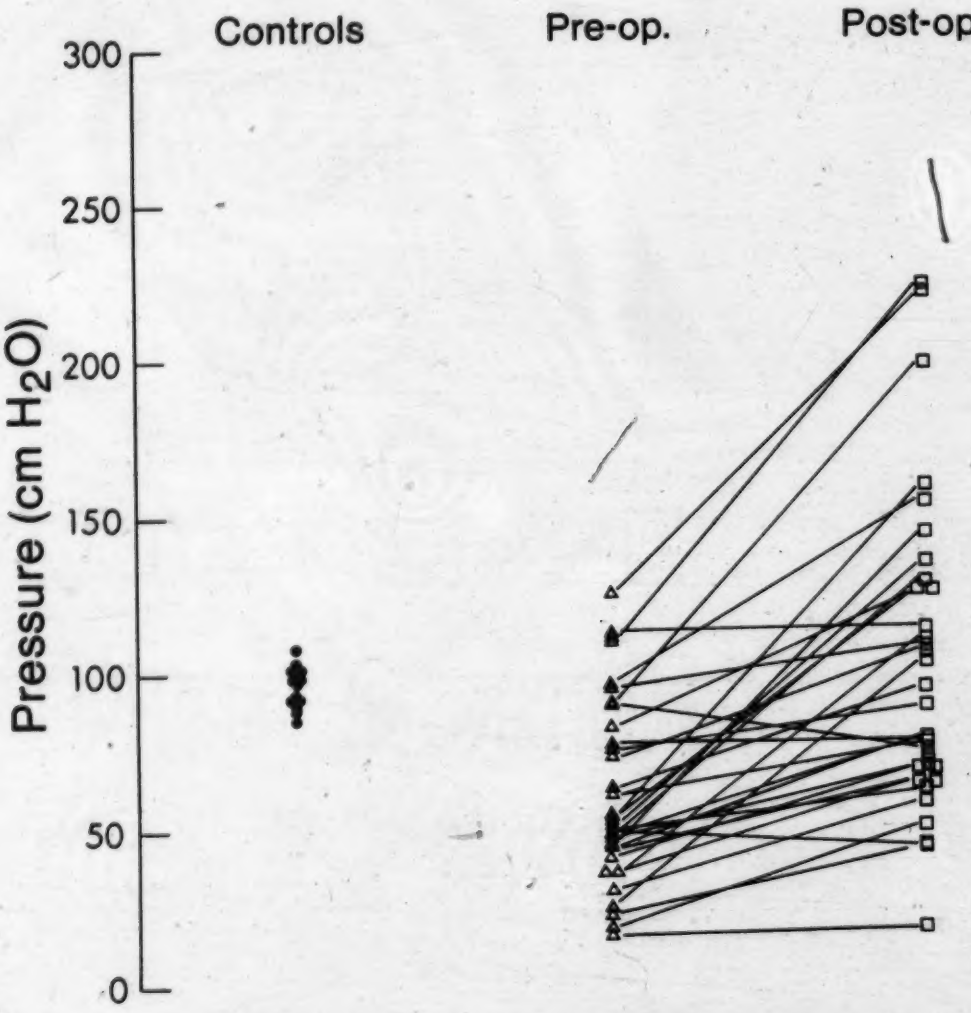
amplitudes observed were not significantly different from those in the control group.

The mean duration of esophageal peristaltic contractions observed at all recording sites in the pre-operative groups were also significantly shorter than those observed in either the control or post-operative groups ($P>0.005$; $P>0.001$ respectively). The duration of contractions observed post-operatively were not significantly different than those observed in the control group.

Aperistaltic contractions were not observed in the control subjects. Eleven patients exhibited aperistaltic activity pre-operatively; eight of these continued to have aperistaltic contractions after surgery. This motor abnormality was observed in nine other patients post-operatively.

FIGURE 9

Amplitude of peristaltic contractions in the lower esophagus in 18 control subjects(●) and 32 patients both pre-(Δ) and post-operatively(□).



Amplitude of peristaltic contractions in the lower esophagus in 18 control subjects (•) and 32 patients both pre-(△) and post-operatively (□).

Relationship of peristaltic amplitudes to R.LESP (Table 23, Fig. 10)

A significant correlation was found betwen the amplitude of distal esophageal peristaltic contractions and the magnitude of resting lower esophageal sphincter pressure. The poorest correlation was observed in the post-operative group.

Relationship of manometric findings to esophagitis (Table 24)

Although those patients with pre-operative esophagitis had lower mean values of R.LESP, C.LESP, and peristaltic amplitudes than those without, the differences were not significant. A similar post-operative improvement was observed in both groups.

Relationship of manometric findings to post-operative dysphagia (Table 25)

Ten patients experienced dysphagia in the post-operative period. The incidence of dysphagia did not relate to post-operative LES pressure, megnitude of residual gradient, amplitude of post-operative contractions, or incidence of aperistaltic contractions.

Table 23

COEFFICIENTS OF CORRELATION (r)

Amplitude of Lower Esophageal Contractions vs

Lower Esophageal Sphincter Pressures at Rest

Sample	n	r	P	Sig
Normals	18	0.42	>0.05	NS
Pre-op.	32	0.33	>0.05	NS
Post-op.	32	0.21	>0.05	NS
Normals + Pre-op.	50	0.50	<0.01	**
Normals + Pre. + Post.	82	0.40	<0.01	**

FIGURE 10

Amplitude of peristaltic contractions in the lower esophagus vs. resting lower esophageal sphincter pressures in 18 control subjects both pre- and post-operatively.

Amplitude of peristaltic contractions in the lower esophagus vs. resting lower esophageal sphincter pressures in 18 control subjects (•) and 32 patients both pre- (△) and post-operatively (□).

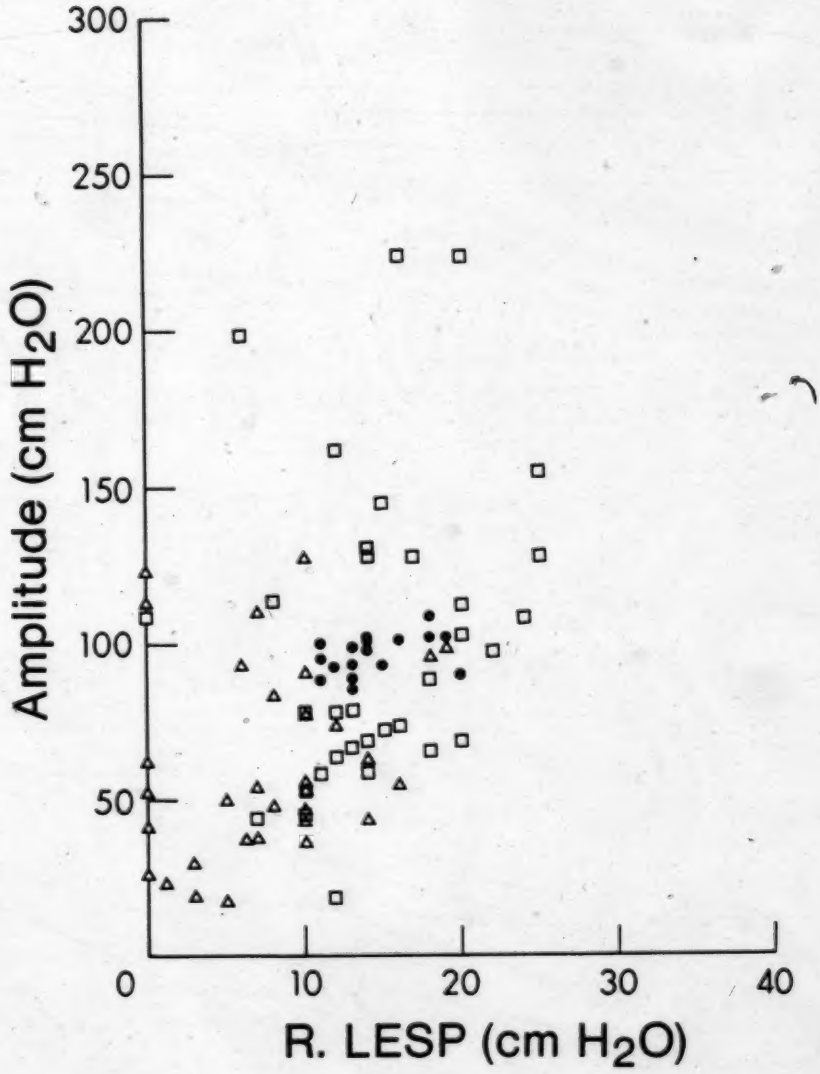


TABLE 24.

Comparison of variables in pre-operative patients with and without esophagitis.

	Esophagitis (n=17)	No esophagitis. (n=15)
R.LESP (cm H_2O)	6.5±4.5	9.0±6.0
C.LESP (cm H_2O)	3.0±5.5	6.5±5.5
Amplitude (cm H_2O)	54±28	69±29
Aperistalsis (percent)	35%	33%

TABLE 25.

Relationship of post-operative dysphagia to manometric findings.

	Dysphagia (n=10)	No dysphagia (n=22)
R.LESP (cm H_2O)	13.9±5.6	15.0±5.8
Residual grad. (cm H_2O)	4.5±4.9	4.2±3.5
Amplitude (cm H_2O)	114±60	97±46
Aperistalsis (percent)	40%	59%

DISCUSSION

Sources of Error

Many factors influence the quantitative measurements obtained by esophageal manometry, and results may vary depending upon the physiological state of the patient, the methodology used, and the observer's interpretation of recordings.

Among patients, hormonal status and the use of drugs are the most important variables[106,107,114]. Otherwise, age, sex and body weight have not shown significant differences in pressure readings obtained. However, the same subject may show both intra-day and day-to-day variations in LES pressure readings[216].

The manometric technique employed and the type of equipment used can influence results. Higher pressure recordings from both the LES and the body of the esophagus are obtained in the supine as against the upright position. Pressures vary with the diameter of the catheter system used, and with both the number and spatial orientation of the catheter openings[49,25]. The length of the catheter system and the rate of catheter perfusion will also influence results[143,146,147]. The size and temperature of the bolus will influence peristaltic amplitudes, and wet swallows produce significantly higher amplitudes than do dry swallows[17,18,216]. The LES pull-through technique used is yet another variable; the stationary method being more reproducable than the rapid pull-through method[25].

Axial movement of the catheter occurs during quiet respiration and swallowing, and the catheter tip may not return to the same position each time, so that a different pressure is recorded[218].

Different methods of interpreting LES pressures may be employed. Respiration is not suspended during a slow pull-through. Thus, pressures may be read at end-inspiration, end-expiration, or at the mean of end-expiratory and end-inspiratory pressures[218].

Considerable intraobserver and interobserver variations occur in determining LES pressure from manometric recordings. Considerable judgement is often required in determining baseline pressure, eliminating artefacts, and in interpreting return to baseline pressure after deglutition[219].

Thus, variation in test protocol, equipment used, and criteria for interpreting tracings may explain the different ranges of results reported from different laboratories. Duranceau et al. have recently reemphasized the importance of each laboratory developing its own control studies to establish the "normal" motility of the population it will study. Further, strict criteria must be employed in the interpretation of results[220].

The studies reported in this work have been carried out in a well-established motility laboratory, and all studies were performed by a single trained nurse. The catheters, perfusion system, perfusion rate and study protocol were identical for all subjects studied, and fixed criteria were used in the interpretation of results. Adherance to such a standardized routine should eliminate most sources of error, and allow reliable discrimination between what is normal and what is abnormal.

Current status of manometry in GE reflux

"The final place of motility studies in the clinical evaluation of patients with gastroesophageal reflux has yet to be determined" -

Duranceau, August, 1983[220]. Castell suggested that routine measurement of LES pressure in GE reflux disease is of little diagnostic value and is impractical[7]. Pope, who pioneered so much of the earlier work on LES pressure measurement, now believes it is time to abandon the use of LES pressure and to develop new intraluminal techniques which can be applied in human studies[218]. He has indeed bitten the hand of the sphincter that has fed him! Pope feels that the vagaries of instrumentation and of intrinsic variablity make LES pressure measurements useless clinically except at extreme values. In reply, Meyer and Castell attempt to defend the clinical value of LES pressure measurement, but stress that this one aspect of diagnostic testing in a patient with potential reflux symptoms should not be overplayed, and that an assessment of esophageal sensitivity to acid, actual esophagitis, and/or an objective measure of the actual reflux should not be excluded in the diagnostic approach to these patients[218].

The consensus of opinion is that an LES pressure below 6mm Hg is highly specific for reflux disease, but has poor sensitivity[4,7,153]. LES pressures also correlate well with endoscopic severity of disease[155].

This study supports these findings, the level below which LES was considered abnormal, i.e., 8 cm H_2O, being equivalent to 6 mm/Hg as quoted by others. Sensitivity levels were similar to other studies, and a correlation with endoscopic severity of disease was also observed. While very low LES measurements were found to be diagnostic of GE reflux, this study supports the view that resting LES pressure measurements alone are too insensitive to be of general diagnostic value.

What diagnostic alternatives are available? The tests that seem at present to be of most potential value are 24 hr distal esophageal pH monitoring[124], and gastroesophageal scintiscanning[171]. As has been pointed out, few centers can afford the expense or the time to employ 24 hr pH monitoring routinely, and it is perhaps best reserved for the most difficult diagnostic problems. Although attractive because of its non-invasive nature, there have been conflicting reports as to the diagnostic value of scintiscanning[171,172]. Thus, the patient with possible GE reflux disease must often face a multitude of tests including radiography, endoscopy, biopsy, potential difference measurements, and standard acid reflux testing.

Abnormal sphincter responses to raised intraabdominal pressure have been well described[88,156]. On the other hand, many workers have not been able to demonstrate an adaptive sphincter response to abdominal compression in humans[208]. The issue remains largely unresolved at the present time[4]. If such an adaptive response existed and was indeed abnormal in GE reflux patients, pull-through measurement of the LES while maintaining abdominal compression may provide another diagnostic index of reflux disease. This "test" has not been previously evaluated in such a context. The results of this study clearly indicate that as a test for GE reflux, sphincter pressure measurement in response to abdominal compression has a similar specificity and greater sensitivity than the measurement of resting sphincter pressure alone. Combining a pull-through of the LES during sustained abdominal compression with resting LES pressure measurement significantly augmented the diagnostic value of LES pressure recordings. It adds little in terms of expense or time to LES manometry, an inflatable pressure cuff about the abdomen

being all the extra equipment required.

Utilizing the same equipment, distal esophageal pressures in response to sudden compression of the abdomen can be assessed. In this study, a "common cavity" between esophagus and stomach was not observed among controls and was considered diagnostic of GE reflux. Significant elevations in distal esophageal pressures did occur among 17% of controls, supporting the impression of Dodds and others that the common cavity test was non-sepcific[4]. These false-positive findings may be explained by eructation, or may be seen if the subject swallows during abdominal compression. However, a sensitivity of 79% and a specificity of 83%, as observed in this study for significant distal esophageal pressure rises, compares favourably with other tests available at the present time, and supports the finding of Butterfield who felt that common cavity testing was a useful adjunct to esophageal manometry[170].

In this laboratory, a tube is incorporated in the manometric catheter assembly for the infusion of acid, and an acid infusion test is readily carried out during the course of a motility study. The criteria for a positive test were different in this study than conventionally used,[157,158] and the test was performed in the supine as against the upright position. Anacid infusion test positive in less than 5 min had high specificity and an acceptable sensitivity. The results of the acid infusion test in this study were similar to the overall results in a review of seven series by Castell[7]. It was of interest that more negative tests were observed during acid infusion in the group with erosive esophagitis. This suggests that some individuals may have a less sensitive esophageal mucosa, allowing a greater degree of structural damage to occur with relatively minor symptoms. Tissue

resistance of the esophagus may be important in determining the effects of reflux, and alkaline reflux esophagitis may account for some of the negative acid infusion tests observed[118,119].

The combination of these four tests, as detailed in this study, provided a high diagnostic yield with excellent specificity for GE reflux. A correlation with the severity of symptoms was not observed. The poorest sensitivity (79%) was observed in those patients with symptomatic GE reflux and normal endoscopy. Viewed from another perspective, a confident diagnosis of reflux was made in 79% of patients in whom an endoscopic diagnosis could not have have been made. A confident diagnosis was also made in 82% of those patients whose resting LES pressures fell in the "grey area", i.e., above 8 cm H_2O. In terms of sensitivity and specificity, these test combinations were at least as accurate as any other test or test combination as yet described. Further, an esophageal motility study per se gives more information about LES dynamics and esophageal motor function than any other test. Finally, this test combination allows an assessment of the potential for reflux (LES pressure measurements), provides objective evidence of actual reflux (common cavity test) and tests esophageal mucosal sensitivity (acid infusion test). The manometric method described is readily performed in the routine clinical setting, and may provide an important research tool in the assessment of medical and surgical treatments.

Current evaluation of diagnostic tests

Diagnostic tests are generally evaluated in terms of their sensitivity in detecting disease, and their specificity in excluding

those without disease. A test showing a sensitivity of 90% and a specificity of 90% is regarded as an excellent test for any given condition. In this study, we have assessed the value of tests in their ability to predict the presence of disease with no other information given about the patient. In order to do this, the frequency with which a given disease occurs in the population (i.e., incidence) must be known. For example, assume that for a disease with a 1% incidence, a given test has 100% sensitivity and 99% specificity. What is the probability of a randomly selected individual with a positive test having the disease? If the population under study is 10,000, then 100 persons with disease will have a positive test, and 100 persons without disease will have a positive test. Thus, a positive test indicates only a 50% probability of having disease. In the same example, if the specificity of the test is only 90%, then 1000 normal people will have a positive test result in these circumstances, indicating that the subject is 10 times more likely to be normal than to have the disease.

This concept may be largely irrelevant in the usual clinical setting, where one undertakes to perform a certain test with a high clinical index of suspicion. However, in a situation where one relies upon a test result to solve a difficult diagnostic problem, high test specificity becomes all important; otherwise, how is one to know whether a patient with a positive test actually has the disease one suspects, or whether the positive result represents a sample of the pool of normal individuals who display a positive result? This is especially true for rare disorders, where test specificity must approach 100% in order to be of diagnostic value. Perhaps other diagnostic tests, not only for GE reflux, but across the diagnostic spectrum, should be examined in this

light.

In this study, this issue is further clouded by the fact that the true indicence of GE reflux is not know. Nebel et al. in a random survey of hospital employees, reported an incidence of daily heartburn in 7%, and of monthly heartburn of 36%[215]. This is not to say that all of these had GE reflux disease, or that people without heartburn do not have GE reflux disease. In assessing the incidence of disease, the population sample is also important. Thus, GE reflux disease may be much more prevalent among patients attending a gastroenterology or cardiology outpatients department than among those attending a dermatology clinic or among the population at large. Clearly, further studies on the prevalence of GE reflux disease are called for.

In this study, three or more positive test responses indicated an almost 100% probability of having GE reflux disease. Two or more positive tests yielded a random probability of around 70% at the 15 to 20% incidence level. Without a precise knowledge of the incidence of GE reflux in the population sampled, final conclusions cannot be drawn.

The role of the LES in the pathogenesis of GE reflux

While a competent LES is regarded as being the main barrier to GE reflux, it is paradoxical that LES pressures are so frequently normal in patients with GE reflux disease. Mechanical factors may play a part in maintaining LES competence, but the LES can function normally without this support[57]. Gastrin and other hormones do not at present appear to play a role in the genesis of LES hypotension[62,63,64]. Different patterns of LES relaxations have been described, and it appears that in

many patients, reflux occurs during transient rises in intraabdominal pressure[105]. There is evidence for a protective mechanism whereby the LES undergoes an adaptive increase in its intrinsic tone as a response to increases in abdominal pressure[88,156]. While vagotomy does not alter resting LES tone, there is evidence that this adaptive response is dependent upon a cholinergic vagovagal reflex, abolished by atropine and by vagotomy[4]. While some workers suggest that the increase in LES pressure observed during abdominal compression can be accounted for by the buttressing effect of intraabdominal pressure on the LES[208], others report much more marked increases in normal subjects, with $\Delta S/\Delta G$ ratios approaching 2[88,156]. There is some evidence for vagal dysfunction in reflux patients[57].

In this study, an adaptive response of the sphincter to raised intraabdominal pressure was observed in most control subjects, and was deficient in most reflux patients, although some overlap did exist. In most normals, the LES pressure recorded during compression was greater than that recorded at rest, and $\Delta S/\Delta G$ ratio was greater than 1. However, these responses were not of the magnitude described by some other workers. In most patients, poor sphincter pressures in response to compression were recorded, $\Delta S/\Delta G$ ratios being less than 1, even if resting LES pressure was normal. These findings suggest that there is indeed a physiological adaptive response to intraabdominal pressure rises associated with the LES, and that this response is defective in a high proportion of patients with GE reflux.

Esophageal motor function in reflux disease

There is now an abundance of evidence to suggest that esophageal motor function can be disturbed by experimentally induced esophagitis[115,116,133]. With the production of esophagitis in the baboon, the ability of the esophagus to clear itself of content was diminished and was related to a weakening in peristaltic amplitude. Esophageal clearance of acid is impaired in reflux patients, and motor abnormalities have been described in patients with severe esophagitis or stricture[129,130,131,132]. Marion et al. describe a patient in whom severe esophagitis and aperistaltic esophagus developed following the ingestion of 100 ml of 25% HCl[221]. These findings persisted for three weeks, but normal peristaltic activity then returned. The findings in this study show that peristaltic amplitudes in all levels of the esophagus are reduced in patients with reflux disease, and an increased incidence of aperistaltic contractions occur. These changes were observed whether there was endoscopic esophagitis present or not. Peristalsis, however, was present in all patients, and the severe degrees of motor incoordination and complete motor failure reported by Olsen[129] and Affholter[130] were not observed. This is probably a reflection of the fact that only 53% of the patients in this study (study B) had endoscopic esophagitis, and no patient in this series had the severe degrees of esophagitis to which major motor abnormalities have been attributed[131]. This is the first study to quantify the motor abnormality in terms of peristaltic amplitudes, and provides evidence that a motor abnormality exists in patients with GE reflux disease even in the absence of gross structural damage.

Is this motor abnormality a primary or secondary phenomenon? It is

appealing to propose that a generalized upper gastrointestinal smooth muscle abnormality exists in reflux disease. Delayed esophageal clearance[127], diminished peristaltic amplitudes, diminished LES tone, and reduced antral motility with delayed gastric emptying support this concept[141]. On the other hand, experimental induction of esophageal motor abnormalities and of hypotonicity of the LES suggest that these motor abnormalities are a secondary phenomenon, and that diminished LES pressures and esophageal peristalsis and clearance are a result of reflux[115,116,133]. In this study, esophageal peristaltic amplitudes returned to normal levels following anti-reflux surgery, again suggesting that reflux was a cause of rather than a result of a smooth muscle abnormality. The mechanism by which this may be induced, especially in the absence of esophagitis, is unclear. The afferent neural pathways from the esophagus are poorly understood, but indirect evidence suggests that a variety of receptors can influence esophageal motor activity[16,17,18]. Perhaps increased mucosal permeability to hydrogen ion may affect motility[116,117]; another possibility is that prostaglandins, released as part of the inflammatory response, may affect esophageal smooth muscle[111].

If reflux does indeed induce a motor abnormality in the body of the esophagus and in the LES, as this and other studies strongly suggest, then it is likely to be a self-perpetuating process. Diminished LES pressure will allow more reflux to occur, and this in turn will diminish esophageal peristalsis and clearance, with further esophageal damage, and further diminution of LES pressure. This study provides evidence to support this "vicious cycle" hypotheses in the early stages of GE reflux disease.

Effect of fundoplication on the LES

Increased resting LES pressures have been well documented following fundoplication[185,186,189,197]. However, the mechanism by which this increase in pressure is achieved is controversial. Some argue that a physiological sphincter has been restored, as reflected in improved sphincter responses to abdominal compression post-operatively[185,206]. It has been suggested that the portion of gastric fundus used in the wrap around may function much as does LES muscle, and may act as a sphincter[57]. Bowes, Butterfield and others argue that creation of a zone of high pressure is not necessary for competence of the gastroesophageal junction following fundoplication, and that recorded zones of elevated pressure may be artifactual and are due to narrowing of the distal esophageal segment; the wrap-around thus provides a purely mechanical buttress for the LES, complemented by the placement of the distal esophageal segment in the positive pressure environment of the abdomen[73,207,208]. In autopsy studies, reflux could not be artificially induced following fundoplication, supporting the concept that a physiological sphincter action is not necessary for GE competence following fundoplication[207]. Incomplete LES relaxation post-operatively has previously been described by Bowes et al., again suggesting mechanical narrowing of the distal esophageal segment[208].

In this study, a significant rise in LES pressure was observed following fundoplication, the mean post-operative pressures being similar to the mean LES pressures in the control group. Sphincter pressures in response to compression were improved in 38% of patients, but remained inadequate in 56% post-fundoplication. Incomplete LES relaxation was again observed post-operatively in this study. This

suggests that mechanical narrowing may prevent complete relaxation, or that at least part of the pressure elevation observed following fundoplication is artifactual. Post-deglutitive sphincter contraction was restored to normal levels post-operatively, and may suggest either a physiological response, or a measurement artifact due to luminal narrowing.

If one accepts that reflux disease in itself can reduce LES pressure, then it is reasonable to argue that surgical prevention of reflux may at least partly restore sphincter function. If LES pressure in response to abdominal compression is a measure of physiological sphincter function, then 38% of post-operative patients as distinct from 9% pre-operatively showed adaptive LES responses to compression, with $\Delta S/\Delta G$ ratios greater than 1. Proximal gastric muscle has very different physiological properties to LES muscle[48], and it is unreasonable to suggest that it can assume sphincter-like properties when wrapped around the distal esophagus. In summary, the main effect of fundoplication is to narrow the distal esophageal segment and externally buttress the LES. By preventing reflux, it may also permit, at least in part, a restoration of physiological sphincter function. Inability of the sphincter to achieve complete relaxation may contribute to gas-bloat like syndromes, but a correlation with post-operative dysphagia was not demonstrated in this study.

Effect of fundoplication on the body of the esophagus

The results of this study indicate that esophageal peristaltic amplitudes are decreased in GE reflux disease, and return to normal after fundoplication. If the motor abnormality observed in reflux

patients was a primary smooth muscle abnormality, it would hardly be corrected by fundoplication. Alternatively, the higher LES pressure, distal esophageal narrowing, and inadequate relaxation of the LES occasioned by fundoplication may call for stronger esophageal peristaltic contractions to propel the ingested bolus into the stomach. A correlation was observed in this study between esophageal peristaltic amplitudes and the magnitude of LES pressure, but the correlation was least valid in the post-operative group. Thus, at least in the post-operative patients, amplitude of peristaltic contractions does not appear to relate to LES pressure, and is therefore not a reflection of distal esophageal obstruction. The improvement in esophageal peristaltic activity following fundoplication is further evidence that abnormal motility seen in reflux patients is a secondary phenomenon.

Aperistaltic activity in the body of the esophagus was observed in 53% of patients post-operatively, as against 34% pre-operatively. Nine patients (28%) only showed aperistaltic activity post-fundoplication. The incidence of this abnormality did not relate to the incidence of endoscopic esophagitis pre-operatively. Thus, there is a paradox where peristaltic contractile amplitudes return to normal, yet increased episodes of aperistaltic contractions occur following fundoplication. Such motor abnormalities have, however, been observed by others following fundopliction[194,205], and it is possible that different mechanisms are involved, this motor incoordination being possibly due to local irritation from dissection, tension on the repair, or loss of distal esophageal fixation[194,205]. Hill claims that these motor abnormalities are corrected by posterior gastropexy, but this matter

requires further study[205]. The low amplitude contractions described by Hill as being associated with aperistalsis and poor esophageal propulsion have not been observed in this study.

CONCLUSION

Three manometric tests of lower esophageal sphincter function have been assessed in combination with an acid infusion test for potential value in the diagnosis of gastroesophageal reflux disease. The results indicate that this protocol can be readily adapted by existing laboratories, is suitable for routine clinical use, provides much information about esophageal motor function, and is at least as accurate in diagnosing GE reflux disease as any other test or combination of tests currently available.

The importance of each laboratory developing its own control studies to establish normal motility patterns for the technique and equipment employed, and the need for strict criteria in the interpretation of results is stressed.

Evidence is presented for the presence of an adaptive response of the lower esophageal sphincter mechanism to increases in intraabdominal pressure in normal subjects. This mechanism is defective in patients with symptomatic gastroesophageal reflux disease. Resting LES pressure measurements alone are of little value in the diagnosis of GE reflux, and LES pressure measurements in response to abdominal compression are more sensitive. The common cavity test was found to be a useful adjunct to esophageal manometry, and provides objective evidence of reflux. New criteria for the interpretation of the acid infusion test have been described, which increase its specificity while retaining acceptable sensitivity.

A new method for evaluating the usefulness of diagnostic tests is presented, and the importance of knowing the incidence of a given

condition in the population when evaluating test specificity is emphasized. The need for further studies to determine the incidence of GE reflux disease is highlighted.

A motor abnormality in the body of the esophagus in patients with GE reflux is described, and evidence is presented that this is a secondary rather than a primary phenomenon. The pathogenesis of GE reflux disease is discussed in terms of this concept.

The effects of fundoplication in restoring gastroesophageal sphincter competence are mainly mechanical, although some return of physiological function is observed post-operatively. The motor defect in the esophagus associated with reflux disease is corrected by fundoplication, although fundoplication itself may induce a separate esophageal motor abnormality.

BIBLIOGRAPHY

1. Skinner, D.B., De Meester, T.R. 1976. Gastroesophageal reflux. Current Problems in Surgery, Vol 13, No. 1.

2. Code, C.F., Schlegel, J.F. 1958. The pressure profile of the gastroesophageal sphincter in man: an improved method of detection. Proc. Mayo Clinic, 33:406-414.

3. Fyke, F.E., Code, C.F., Schlegel, J.F. 1956. The gastroesophageal sphincter in healthy human beings. Gastroenterologia, 86:135-150.

4. Dodds, W.J., Hogan, W.J., Helm, J.F., Dent, J. 1981. Pathogenesis of reflux esophagitis. Gastroenterology, 81:376-94.

5. Nissen, R. 1961. Gastropexy and "fundoplication" in surgical treatment of hiatal hernia. Am.J.Dig.Dis. 6:954.

6. Fisher, R.S., Cohen, S. 1978. Gastroesophageal reflux. Medical Clinics of North America, 62:3-20.

7. Richter, J.E., Castell, D.O. 1982. Gastroesophageal reflux: Pathogenesis, diagnosis and therapy. Ann.Int.Med. 97:93-103.

8. Cohen, S., Snape, W.J. 1978. The pathophysiology and treatment of gastroesophageal reflux disease. Arch.Intern.Med. 138:1398-1401.

9. Vantrappen G., Hellemans, J. 1974. Diseases of the esophagus. New York, Springer-Verlog, pp. 1-38.

10. Kaufmann, P., Lierse, W., Stark, J., Stelyner, F. 1968. Die Muskelanordnung in der Speiserohre (Mensch, Rhesusaffe, Kaninchen, Maus, Ratte, Sechund). Ergebn.Anat.Entwickl.Gesch. 40:3-33.

11. Botha M. 1962. The Gastroesophageal Junction; Churchill, London.

12. Aylwin, J.A. 1953. The physiological basis of reflux esophagitis in sliding hiatal diaphragmatic hernia. Thorax. 8:38.

13. Bombeck, C.T., Dillard, D.H., Nyhus, L.M. 1966. Muscular anatomy of the gastroesophageal junction and the role of phrenoesophageal ligament: autopsy study of sphincter mechanism. Ann.Surg. 164:643-654.

14. Skinner, D.B., Belsey, R.H., Hendrix, T.R., Zuidema, G.D., eds.; 1972. Gastroesophageal Reflux and Hiatal Hernia. Little, Brown & Co., Boston, Mass.

15. Barrett, N.R. 1957. The lower esophagus lined by columnar epithelium. Surgery 41:881.

16. Mei, N., Aubert, M., Crousillat, J., Ranieri, F. 1974. Sensory innervation of the lower esophagus of the cat. Comparison with the other parts of the digestive system. In: Proceedings of the Fourth International Symposium on Gastrointestinal Motility, Daniel, E.E. (ed.); Mitchell Press Ltd., Vancouver, Canada.

17. Creamer, B., Schlegel, J. 1957. Motor responses of the esophagus to distention. J.Appl.Physiol. 10:498-504.

18. Wallin, L., Boesley, S., Madsen, T. 1978. The effect of HCl infusion in the lower part of the esophagus on the pharyngo-esophageal sphincter pressure in normal subjects. Scand.J.Gastroenterology 13:821-826.

19. Doty, R.W. 1976. Neural organization of deglutition. In: Handbook of Physiology, Code, C.F., Heidel, W.(eds.); Sec. 6, Vol. 4. Williams and Wilkins, Baltimore.

20. Inglefinger, F.J. 1958. Esophageal motility. Physiol.Rev. 38:533-584.

21. Goyal, R.K., Cobb, B.W. 1981. Motility of the pharynx, Esophagus, and Esophageal Sphincters. In: Physiology of the Gastrointestinal Tract. Johnson, L.R. (ed.); Raven Press, New York, New York.

22. Fleshler, B., Hendrix, T.R., Kramer, P., Inglefinger, F.J. 1959. The characteristics of 1° and 2° peristalsis in the esophagus. J.Clin.Invest. 38:110-116.

23. Seigel, C.,I., Hendrix, T.R. 1961. Evidence for the central mediation of secondary peristalsis in the esophagus. Bull. Johns Hopkins Hosp. 108:297-307.

24. Cohen, S. 1979. Motor disorders of the esophagus. N.Engl.J.Med. 301:184-192.

25. Welsh, R.W., Drake, S.T. 1980. Normal lower esophageal sphincter pressure: a comparison of rapid vs slow pull-through techniques. Gastroenterology:78:1446-1451.

26. Harris, L.D., Pope, C.E. II. 1966. The pressure inversion point: its genesis and reliability. Gastroenterology. 51:641-648.

27. Itoh, I., Aizawa, I., Honda, R., Hiratashi, H., Couch, E.F. 1978. Control of lower esophageal sphincter contractile activity by motilin in conscious dogs. Am.J.Dig.Dis. 23:341-345.

28. Pommerenke, W.T. 1928. A study of the sensory areas eliciting the swallowing reflex. Am.J.Physiol. 84:36-41.

29. Botha, G.S.M. 1962. The gastro-oesophageal junction. Little, Brown. Boston.

30. Doty, R.W., Richmond, W.H., Storey, A.T. 1967. Effects of medullary lesions on coordination of deglutition. Exp.Neurol. 17:91-106.

31. Ler, C.S., Flanegan, J.B., Moorrees, C.F. 1965. The frequency of deglutition in man. Arch.Oral.Biol. 10:83-99.

32. Doty, R.W. 1968. Neural organization of deglutition. In: Handbook of Physiology, section 6, Alimentary Canal, Volume IV; Motility: 1861-1902, American Physiological Society, Washington, D.C.

33. Asoh, R., Goyal, R.K. 1978. Manometry and electromyography of the upper esophageal sphincter in the opossum. Gastroenterology, 74:514-520.

34. Horwitz, A.L., Nelson, J.A., Haddad, J.K. 1975. Oropharyngeal dysphagia: manometric and cineesophagographic findings. Am.J.Dig.Dis. 20:313-324.

35. Lawn, A.M. 1964. The localization by means of electrical stimulation of the origin and path in the medulla oblongata of the motor nerve fibres of the rabbit esophagus. J.Physiol.(Lond.) 174:232-244.

36. Roman, C. 1966. Nervous control of peristalsis in the esophagus. J.Physiol.(Paris) 58:79-108.

37. Winship, D.H., DeAndrade, S.R., Zboralske, F.F. 1970. Influence of bolus temperature on human esophageal motor function. J.Clin.Invest. 49:243-250.

38. Jordan, P.H., Longhi, E.H. 1971. Relationship between size of bolus and the act of swallowing on esophageal peristalsis in dogs. Proc.Soc.Exp.Biol.Med. 137:868-871.

39. Janssens, J., DeNever, I., Vantrappen, G., Hellemans, J. 1976. Peristalsis in smooth muscle esophagus after transection and bolus deviation. Gastroenterology 67:245-251.

40. Mukhopadhyay, A.K., Weisbrodt, N.W. 1975. Neural organization of esophageal peristalsis: role of the vagus nerve. Gastroenterology 58:444-447.

41. El-Sharkawy, T.Y., Diamant, N.E. 1976. Contraction patterns of esophageal circular smooth muscle induced by cholinergic excitation. Gastroenterology (Abst) 70:969.

42. Weisbrodt, N.W., Christensen, J. 1972. Gradient of contractions in the opossum esophagus. Gastroenterology 62:1159-1166.

43. Goyal, R.K., Gidda, J.S. 1981. Relationship between electrical and mechanical activity in the opossum esophagus. Am.J.Physiol. 302:609-615.

44. Diamant, N.E., El-Sharkawy, T.Y. 1977. Neural control of esophageal peristalsis. Gastroenterology 72:546-556.

45. Lund, C.F., Christensen, J. 1969. Electrical stimulation of esophageal smooth muscle and the effects of antagonists. Am.J.Physiol. 217:1369-1374.

46. Dodds, W.J., Christensen, J., Dent, J., Wood, J.D., Arndorfer, R.C. 1978. Esophageal contractions induced by vagal stimulation in the opossum. Am.J.Physiol. 235:E392-E401.

47. Christensen, J., Lund, C.F. 1969. Esophageal responses to distension and electrical stimualtion. J.Clin.Invest. 48:408-419.

48. Christensen, J., Conklin, J.L. 1973. Studies on the origin of the distinctive mechanics of smooth muscle at the esophagogastric junction. Proceedings of the Fourth International Symposium on Gastrointestinal Motility, Bannf, Alberta, Canada, 63-71.

49. Biancani, P., Zabinski, M.P., Behar, J. 1975. Pressure, tension, and force of closure of the human lower esophageal sphincter and esophagus. J.Clin.Invest. 56:476-83.

50. Weisbrodt, N.W., Lee, S.J. 1977. Metabolic factors which influence esophageal smooth muscle. Gastroenterology (Abst) 72:A-125.

51. Daniel, E.E., Taylor, G.S., Holman, M.E. 1976. The myogenic basis of active tension in the lower esophageal sphincter. Gastroenterology (Abst) 70:874.

52. Goyal, R.K., Rattan, S. 1980. Effects of sodium nitroprusside and verapramil on lower esophageal sphincter. Am.J.Physiol. 238:G40-44.

53. Meissner, A.J., Bowes, K.L., Zwick, R., Daniel, E.E. 1976. Effect of motilin on the lower esophageal sphincter. Gut 17:925-32.

54. Lind, J.F., Crispin, J.S., McIver, D.K. 1968. The effect of atropine on the lower esophageal sphincter. Can.J.Physiol.Pharmacol. 46:233-8.

55. Zfass, A.M., Prince, R., Allen, F.N. 1970. Inhibitory beta-adrenergic receptors in the human distal esophagus. Am.J.Dig.Dis. 55:303-10.

56. Mazur, J.M., Skinner, D.B., Jones, E.L. 1973. Effect of transabdominal vagotomy on the human gastroesophageal high pressure zone. Surgery 73:818-22.

57. Castell, D.O. 1975. The Lower Esophageal Sphincter. Physiologic and Clinical Aspects. Ann.Int.Med. 83:390-401.

58. Rattan, S., Goyal, R.K. 1974. Neural control of the lower esophageal sphincter. J.Clin.Invest. 54:899-906.

59. Christensen, J., Freeman, B.W., Miller, J.K. 1973. Some physiological characteristics of the esophagogastric junction in the opossum. Gastroenterology 64:1119-1125.

60. Blackman, A.H., Nasrullah, M., Thayer, W.R. 1971. Transabdominal vagectomy and lower esophageal sphincter function. Arch.Surg. 102:6-8.

61. Goyal, R.K., Rattan, S. 1975. Nature of the vagal inhibitory innervation to the lower esophageal sphincter. J.Clin.Invest. 55:119-26.

62. Castell, D.O., Harris, L.D. 1970. Hormonal control of gastroesophageal sphincter strength. N.Eng.J.Med. 282:886-889.

63. Sturdevant, R.A.L. 1974. Is gastrin the major regulator of lower esophageal sphincter pressure? Gastroenterology 67:551-3.

64. Farrell, R.L., Castell, D.O., McGuigan, J.E. 1974. Measurements and comparisons of lower esophageal sphincter pressures and serum gastrin levels in patients with gastroesophageal reflux. Gastroenterology 67:415-422.

65. Dodds, W.J., Hogan, W.J., Miller, W.N. 1976. Reflux esophagitis. Dig.Dis. 21:49-67.

66. Tocornal, J.A., Snow, H.D., Fonkalstrud, E.W. 1968. A mucosal flap-valve mechanism to prevent gastroesophageal reflux and esophagitis. Surgery 64:519-23.

67. Watkins, D.H., Preedel, A.E., Munro, G.A. 1954. Valvular esophagogastrostomy. Surgical Forum, p. 328. Saunders & Co.

68. Barret, N.R. 1952. Discussion on hiatus hernia. Proc.Roy.Soc. 45:279.

69. Jackson, C. 1922. The diaphragmatic pinchcock in so-called "cardiospasm". Laryngoscope 32:139.

70. Friedland, G.W., Melcher, D.H., Berridge, F.R., Gresham, G.A. 1966. Debatable points in the anatomy of the lower esophagus. Am.J.Roent. 21:487-98.

71. Gicular, A., Cohan, B., Zimmerman, A., Kark, E.A. 1967. The significance of an intraabdominal segment of canine esophagus as a competent anti-reflux mechanism. Surgery 61:784-790.

72. Inglefinger, F.J. 1971. The sphincter that is a sphinx. N.Engl.J.Med. 284-1095-1096.

73. O'Sullivan, G.C., DeMeester, T.R. Joelsson, B.E., Smith, R.B., Blough, R.R., Johnson, L.F., Skinner, D.B. 1982. Interaction of lower esophageal sphincter pressure and length of sphincter in the abdomen as determinants of gastroesophaeal competence. Am.J.Surg. 143:40-47.

74. Lind, J.F., Warrian, W.G., Wankling, W.J. 1966. Responses of the gastroesophageal junctional zone to increases in abdominal pressure. Can.J.Surg. 9:32-40.

75. Cohen, S., Harris, L.D. 1969. The adaptive response of the lower esophageal sphincter. Clin.Res.(Abst) 17:300.

76. Crispin, J.S., McIver, D.K. Lind, J.F. 1967. Manometric study of the effect of vagotomy on the lower esophageal sphincter. Can.J.Surg. 10:299-303.

77. Lind, J.F., Crispin, J.S., McIver, D.K. 1968. The effect of atropine on the gastroesophageal sphincter. Can.J.Physiol.Pharmacol. 46:233-238.

78. Cohen, S., Harris, L.D. 1971. Does hiatus hernia affect competence of the gastroesophageal sphincter? New Engl.J.Med. 284:1053-1056.

79. Dodds, W.J., Hogan, W.J., Steff, J.J. 1975. Effect of increased intrabdominal pressure on lower esophageal sphincter pressure. Am.J.Dig.Dis. 20:298-308.

80. Kaye, M.D. 1977. Post-prenatal gastro-esophageal reflux in healthy people. GUT 18:709-712.

81. Demeester, T.R., Johnson, L.F., Guy, J.J., Toscano, M.S., Hall, A.W., Skinner, D.B. 1076. Patterns of gastroesophageal reflux in health and disease. Ann.Surg. 184:459-470.

82. Naef, A.P., Savary, M., Ozzello, L., Pearson, F.G. 1975. Columnar-lined lower esophagus: an acquired lesion with malignant predisposition. J.Thorac.Cardiovas.Surg. 70:826-835.

83. Bowditch, H.I. 1853. A Treatise on Diaphragmatic Hernia. Buffalo: Jewett, Thomas.

84. Winklestein, A. 1935. Peptic esophagitis: a new clinical entity. J.Amer.Med.Assoc. 104:906-909.

85. Allison, P.R. 1945. Peptic ulcer of the esophagus. J.Thor.Surg. 308-317.

86. Allison, P.R. 1951. Reflux esophagitis, sliding hiatal hernia, and the anatomy of repair. Surg.Gynecol.Obstet. 92:419-431.

87. Hiebert, C.A. 1977. The recognition and management of gastroesophageal reflux without hiatal hernia. World J.Surg. 1:445-451.

88. Cohen, S., Harris, L.D. 1971. Does hiatus hernia affect competence of the gastroesophageal sphincter? New Eng.J.Med. 284:1053-1056.

89. Atkinson, M., Edwards, D.A.W., Honour, A.J., Rowlands, E.N. 1957. The esophagogastric sphincter in hiatus hernia. Lancet Dec: 1138-1142.

90. Hiebert, C.A. 1970. Primary incompetence of the gastric cardia. Am.J.Surg. 119:365-371.

91. Skinner, D.B. 1966. Symptomatic esophageal reflux. Am.J.Dig.Dis. 2:771.

92. Belsey, R. 1960. The pulmonary complications of esophageal disease. Brit.J.Dis.Chest 54:342.

93. Heil, T., Mattes, P., Loeprecht, H. 1980. Gastro-esophageal reflux: an aetiological factor for bleeding in oesophageal varices? Br.J.Surg. 67:467-468.

94. Eckardt, V.F., Grace, N.D. 1979. Gastroesophageal reflux and bleeding esophageal varices. Gastroenterology 76:39-42.

95. Quincke, H. 1897. Ulcus oesophagi ex digestione. Deutsch.Arch.Klin.Med. 24:72.

96. Hendrix, T.R., Yardley, J.H. 1976. Consequences of gastro-oesophageal reflux. Clin.Gastroenterol. 5:155-174.

97. Seefeld, U., Krejs, G.J., Siebenmann, R.E., Blum, A.L. 1977. Esophageal histology in gastroesophageal reflux. Dig.Dis. 22:956-964.

98. Ismail-Beigi, F., HOrton, P.F., Pope, C.E. 1970. Histological consequences of gastroesophageal reflux in man. Gastroenterology 58:163-175.

99. Behar, J., Sheahan, D.C. 1975. Histologic abnormalities in reflux esophagitis. Arch.Path. 99:287-391

100. Sandry, R.J. 1962. The pathology of chronic esophagitis. GUT 3:189-200.

101. Barret, N.R. 1950. Chronic peptic ulcer of the oesophagus and "oesophagitits". Br.J.Surg. 38:175-182.

102. Mossberg, S.M. 1966. The columnar-lined esophagus (Barrett Syndrome) an acquired condition. Gastroenterology 50:671-676.

103. Pope, C.E., Meyer, G.W. Castell, D.O. 1981. Is measurement of lower esophageal sphincter pressure clinically useful? Dig.Dis.Sci. 26:1025-1031.

104. Haddad, J.K. 1970. Relastion of gastroesophageal reflux to yield sphincter pressures. Gastroenterology 58:175-84.

105. Dent, J., Dodds, W.J., Friedman, R.H. 1980. Mechanism of gastroesophageal reflux in asymptomatic recumbent human beings. J.Clin.Invest. 65:256-67.

106. Kaminetzky, H.A. 1969. In: Medical Complications During Pregnanacy; ed., D.M. Hayes. McGraw Hill.

107. van Thiel, D.H., Gavaler, J.S., Stremple, J. 1976. Lower esophageal sphincter pressure in women using sequential oral contraceptives. Gastroenterology 71:232-234.

108. Cohen, S., Lipshutz, W. 1971. Hormonal regulation of human lower esophageal sphincter strength: interaction of gastrin and secretin. J.Clin.Invest. 50:449-454.

109. Resin, H., Stern, D.H., Sturdevant, R.A. 1973. Effect of the C-terminal octapeptide of cholecystokinin on lower esophageal sphincter pressure in man. Gastroenterology 64:946-949.

110. Jaffer, S.S., Makhlouf, G.M., Schorr, B.A. 1974. Nature and kinetics of inhibition of lower esophageal sphincter pressure by glucagon. Gastroenterology 67:42-46.

111. Goyal, R.K. Mukhopadhyay, A., Rattan, S. 1974. Effect of prostaglandin E_2 on the lower esophageal sphincter in normal subjects and patients with achalasia (abst.) Clin.Res. 22:358.

112. Hogan, W.J., Viegas de Andrade, S.R.T., Winship, D.H. 1972. Ethanol induced acute esophageal motor dysfunction. J.Appl.Physiol. 32:755-60.

113. Dennish, G.W., Castell, D.O. 1971. Inhibitory effect of smoking on the lower esophageal sphincter. N.Engl.J.Med. 284:1136-7.

114. Castell, D.O. 1975. The lower esophageal sphincter. Physiologic and clinical aspects. Ann.Intern.Med. 83:390-401.

115. Eastwood, G.L., Castell, D.O., Higgs, R.H. 1975. Experimental esophagitis in cats impairs lower esophageal sphincter pressure. Gastroenterology 69:146-53.

116. Higgs, R.H., Castell, D.O., Eastwood, G.L. 1976. Studies on the mechanism of esophagitis induced lower esophageal sphincter hypotension in cats. Gastroentology 71:51-7.

117. Goldberg, H.L., Dodds, W.J., Jec, S. 1969. Role of acid and pepsin in acute experimetnal esophagitis. Gastroenterology 56:223-30.

118. Henderson, R.D., Mugashe, F.L., Jeejeebhoy, K.D., Sycypanski, M.M., Cullen, J., Marryatt, G., Boszko, A. 1973. Synergism of acid and bile salts in the production of experimental esophagitis. Can.J.Surg. 16:12-17.

119. Safaie-Shirayi, S., DenBesten, L., Zike, W.L. 1975. Effect of bile salts on the ionic permeability of the esophageal mucosa and their role in the production of esophagitis. Gastroenterology 68:728-733.

120. Khamis, B., Kennedy, C., Finucane, J., Stephen-Doyle. 1978. Transmucosal potential difference; diagnositc valve in gastro-oesophageal reflux. GUT 19:396-398.

121. Turner, K.S., Powell, D.W., Carney, C.N., Orlando, R.C., Bozymski, E.M. 1978. Transmural electrical potential difference in the mammalian esophagus in vivo. Gastroenterology 75:286-291.

122. Malhotra, S.L. 1979. New approaches to the pathogensis of peptic ulcer based on the protective action of saliva. Amer.J.Dig.Dis. 15:489-496.

123. Goldberg, H.I., Dodds, W.J., Montgomery, C. 1970. Controlled production of acute esophagitis. Invest.Radiol. 5:254-6.

124. Johnson, L.F., DeMeester, T.R. 1974. Twenty-four hour pH monitoring of the distal esophagus: a quantitative measure of gastroesophageal reflux. Am.J.Gastroenterol. 62:325-32.

125. Spencer, J. 1969. Prolonged pH recording in the study of gastro-oesophageal reflux. Brit.J.Surg. 56:912-914.

126. Atkinson, M., Van Gelder, A. 1977. Esophageal intraluminal pH recordings in the assessment of gastroesophageal reflux and its consequences. Dig.Dis. 22:365-370.

127. Stanciu, C., Bennett, J.R. 1974. Oesophageal acid clearance; one factor in the production of reflux oesophagitis. GUT 15:852-7.

128. Helm, J.F., Dodds, W.J., Riedel, D.R., Teeter, B.C., Hogan, W.J., Arndorfer, R.C. 1983. Determinants of esophageal acid clearance in normal subjects. Gastroenterology 85:607-12.

129. Olsen, A.M., Schlegel, J.F. 1965. Motility disturbances caused by esophagitis. J.Thorac.Cardiovasc.Surg. 50:607-612.

130. Attolter, H. 1966. Pressure characteristics of reflux esophagitis. Helv.Med.Act. 5:395-402.

131. Henderson, R.D., Mugashe, F., Jeejeebhoy, K.N., Cullen, J., Boszko, A., Sycpanski, M., Marryatt, G. 1974. The motor defect of esophagitis. Can.J.Surg. 17:112-116.

132. Ahtaridis, G., Snape, W.J., Cohen, S. 1979. Clinical and manometric findings in benign peptic strictures of the esophagus. Dig.Dis.Sci. 24:858-61.

133. Sinar, D.R., Fletcher, J.R., Cordova, C.C., Eastwood, G.L., Castell, D.O. 1981. Acute acid-induced esophagitis impairs esophageal peristalsis in baboons (Abst). Gastroenterology 80:1286.

134. McCallum, R.W., Berkowitz, D.M., Lerner, E. 1981. Gastric emptying in patients with gastroesophageal reflux. Gastroenterology 80:285-91.

135. McCallum, R.W., Mensh, R., Lange, R. 1982. Definition of Gastric Emptying Abnormality Present in Gastroesophageal Reflux Patients. Motility of the Digestive Tract; Weinbeck, M., ed., Raven Press, New York.

136. Gatzinsky, P., Granerus, G., Sandberg, N. 1980. Gastric acid secretion (GAS) and hiatal hernia. Acta.Chir.Scand. 146:583-595.

137. Matikainen, M. 1981. Gastric acid secretion, oesophageal acid reflux, and oesophagitis in patients with symptomatic gastro-oesophageal reflux. Scand.J.Gastroenterol. 16:1043-1048.

138. Kaye, M.D., Showalter, J.P. 1974. Pyloric incompetence in patients with symptomatic gastroesophageal reflux. J.Lab.Clin Med. 83:198-206.

139. Stol, D.W., Murphy, G.W., Collis, J.L. 1974. Duodeno-gastric reflux and acid-secretion in patients with symptomatic hiatal hernia. Scand.J.Gastrroenterol. 9:97-101.

140. Donovan, I.A., Harding, L.K., Keighley, M.R.B., Griffin, D.W., Leight Collis, J. 1977. Abnormalities of gastric emptying and pyloric reflux in uncomplicated hiatus hernia. Brit.J.Surg. 64:847-848.

141. Behar, J., Rambsy, G. 1978. Gastric emptying and antral motility in reflux esophagitis. Gastroenterology 74:253-256.

142. Meltzer, J.S. 1894. Recent experimental contributions to the physiology of deglutition. New York Med.J. 59:389.

143. Pope, C.E. 1967. A dynamic test of sphincter strength: its application to the lower esophageal sphincter. Gastroenterology 52:779-786.

144. Winans, C.S., Harris, L.D. 1967. Quantitation of lower esophageal sphincter competence. Gastroenterology 52:773-778.

145. Cohen, S., Harris, L.D. 1970. Lower esophageal sphincter pressure as an index of lower esophageal sphincter strength. Gastroenterology 58:157-162.

146. Zabinski, M.P., Spiro, H.M., Biancani, P. 1975. Influence of perfusion rate and compliance on esophageal manometry. J.Appl.Physiol. 38:177-180.

147. Arndorfer, R.C., Stef, J.J., Dodds, W.J., Linehan, J.H., Hogan, W.J. 1977. Improved infusion system for intraluminal esophageal manometry. Gastroenterology 73:23-27.

148. Weihrauch, T.R. 1981. Esophageal Manometry. Urban and Schwargenberg, Baltimore

149. Haddad, J.K. 1970. Relation of gastroesophageal reflux to yield sphincter pressures. Gastroenterology 58:175-84.

150. Benz, L.J., Hootkin, L.A., Marguilies, S., Donner, M.W., Cauthorne, R.T., Hendrix, T.R. 1972. A comparison of clinical measurements of gastroesophageal reflux. Gastroenterology 62:1-5.

151. Behar, J., Biancani, P., Sheahan, D.G. 1976. Evaluation of esophageal tests in the diagnosis of reflux esophagitis. Gastroenterology 71:9-15.

152. Stanciu, C., Hoare, R.C., Bennett, J.R. 1977. Correlation betwen manometric and pH tests for gastroesophageal reflux. Gut 18:536-40.

153. Winans, C.S. 1978. Diagnostic evaluation of esophageal function. Proceedings of the Second International Symposium on the Esophagus and Gastroesophageal Junction. Ixtapa, Mexica, pp 25-30

154. Ahtaridis, G., Snape, W.J. Cohen, S. 1981. Lower esophageal sphincter pressure as an index of gastroesophageal acid reflux. Dig.Dis.Sci. 26:993-8.

155. Welch, R.W., Luckmann, K., Ricks, P., Drake, S.T., Bannayan, G., Owensby, L. 1980. Lower esophageal sphincter preesure in histologic esophagitis. Dig.Dis.Sci. 25:420-6.

156. Lind, J.F., Warrian, W.G., Wankling, W.J. 1966. Responses of the gastroesophageal junctional zone to increases in abdominal pressure. Can.J.Surg. 9:32-38.

157. Bernstein, L.M. Baker, L.A. 1958. A clinical test for esophagitis. Gastroenterology 34:760-81.

158. Wiman, G.R., Meyer, C.T., McCallum, R.W. 1982. Interpretation of the Bernstein Test: a reappraisal of criteria. Ann.Int.Med. 96:320-322.

159. Dyer, M.H., Pridie, R.B. 1968. Incidence of hiatus hernia in asymptomatic subjects. Gut 9:696-9.

160. Donner, M.W., Silbiger, M.L., Hookman, P., Hendrix, T.R. 1966. Acid barium swallows in the radiographic evaluation of clinical esophagitis. Radiology 87:220-5.

161. Linsman, J.F. 1965. Gastroesophageal reflux elicited while drinking water - (water siphonage test): its clinical correlation with pyrosis. Am.J.Roentgenol.Rodium.Ther.Nuc.Med. 94:325-32.

162. Skucas J., Schrank, W.W. 1975. The routine air-contrast examination of the esophagus. Radiology 115:482-4.

163. Ott, D.J., Wu, W.C., Gelfand, G.W. 1981. Reflux esophagitis revisited:prospective analysis of radiologic accuracy. Gastrointet.Radiol. 6:1-7.

164. Behar, J. 1976. Reflux esophagitis: pathogenesis, diagnosis and management. Arch.Intern.Med. 136:560-6.

165. Weinstein, W.M., Bogoch, E.R., Bowes, K.L. 1975. The normal human esophageal mucosa: a histological reappraisal. Gastroenterology 68:40-44.

166. Tuttle, S.G., Grossman, M.I. 1958. Detection of gastroesophageal reflux by simultaneous measurement of intraluminal pressure and pH. Proc.Soc.Exp.Biol.Med. 98:225-7.

167. Skinner, D.B., Booth, D.J. 1970. Assessment of distal esophageal function in patients with hiatal hernia and/or gastroesophageal reflux. Ann.Surg. 172:627-37.

168. Ahtaridis, G., Snape, W.J., Cohen, S. 1981. Lower esophageal sphincter pressure as an index of gastroesophageal acid reflux. Dig.Dis.Sci. 26:993-8.

169. Battle, W.S., Nyhus, L.M., Bombeck, C.T. 1973. Gastroesophageal reflux: diagnosis and treatment. Ann.Surg. 177:560-5.

170. Butterfield, D.G., Struther, J.E., Showalter, J.P. 1972. A test of gastroesophageal sphincter competence:the common cavity test. Dig.Dis. 5:415-421.

171. Fisher, R.S. Malmud, L.S., Roberts, G.S., Lobis, I.F. 1976. Gastroesophageal (GE) scintiscanning to detect and quantitate GE reflux. Gastroenterology 70:301-8.

172. Hoffman, G.C., Vansant, J.H. 1979. The gastroesophageal scintiscan: comparison of methods to detect gastroesophageal reflux. Arch.Surg. 114:727-8.

173. Miller, W.N., Ganeshappa, K.P., Dodds, W.J., Hogan, W.J., Barresas, R.F., Arndorfer, R.C. 1977. Effect of bethanechol on gastroesophageal reflux. Am. J. Dig. Dis. 22:230-4.

174. Thanik, K.D., Chey, W.Y., Shan, A.N., Gutierrey, J.G. 1980. Reflux esophagitis: effect o bethanechol on symptoms and endoscopic findings. Ann.Intern.Med. 93:805-8.

175. McCallum, R.W., Kline, M.M., Curry, N., Sturdevant, R.A.L. 1975. Comparative effects of metoclopramide and bethanechol on lower esophageal sphincter pressure in reflux patients. Gastroenterology 68:1114-8.

176. Bright-Asare, P., El-Bassoussi, M. 1980. Cimetidine, metoclopramide, or placebo in the treatment of symptomatic gastroesophageal reflux. J.Clin.Gastroenterol. 2:149-56.

177. Powell-Jackson, P., Barkley, H., Northfield, T.C. 1978. Effect of cimetidine in symptomatic gastro-oesophageal reflux. Lancet. 32:1068-9.

178. Graham, D.Y., Lanza, F., Dorsch, E.R. 1977. Symptomatic reflux esophagitis: a double-blind controlled comparison of antacids and alginate. Curr.Ther.Res. 22:653-8.

179. Harrington, S.W. 1928. Diaphragmatic hernia. Arch.Surg. 16:386.

180. Collis, J.L., Kelly, T.D., Wiley, A.N. 1954. Anatomy of the erura of the diaphragm and the surgery of hiatus hernia. Thorax. 9:175.

181. Boerema, I., Germs, R. 1955, Fixation of the lesser curvature of the stomach to the anterior abdominal wall after reposition of the hernia through the esophageal hiatus. Arch.Chir.Neerl. 7:351.

182. Skinner, D.B., Belsey, R.H.R. 1967. Surgical management of esophageal reflux and hiatus hernia. J.Thorac.Cardiovasc.Surg. 53:33.

183. Hill, L.D. 1967. An effective operation for hiatal hernia: an eight year appraisal. Ann.Surg. 166:681.

184. Hill, L.D. 1972. Surgery and gastroesophageal reflux. Gastroenterology 63:183.

185. DeMeester, T.R., Johnson, L.F., Kent, A.H. 1974. Exaluation of current operations for the prevention of G.E. reflux. Ann.Surg. 180:511-525.

186. Dilling, E.W., Peyton, M.D., Cannon, J.P., Kanaly, P.J., Elleins, R.C. 1977. Comparison of nissen fundoplication and belsey mark IV in the management of gastroesophageal reflux. Am.J.Surg. 134:730-733.

187. Wilson, M.G., Bailey, I.S., Penry, A.B. 1974. The surgical treatment of reflux esophagitis: results of surgical rjepair over a 12-year period.

188. Battle, W.S., Nyhus, L.M., Bombeck, C.T. 1973. Nissen fundoplication and esophagitis secondary to gastroesophageal reflux. Arch.Surg. 106:588-592.

189. Shah, I.K., Daniel, O. 1972. The results of fundoplication for the relief of oesophageal reflux due to hiatus hernia. Brit.J.Surg. 59:285-287.

190. Ellis, F.H., Garabedian, M., Gibb, S.P. 1973. Fundoplication for gastroesophageal reflux. Arch.Surg. 107:186-192.

191. Bushkin, F.L., Neustein, C.L., Parker, T.H., Woodward, E.R. 1977. Nissen fundoplication for reflux peptic esophagitis. Ann.Surg. 185:672-677.

192. Rossetti, M., Hell, K. 1977. Fundopliction for the treatment of gastroesophageal reflux in hiatal hernia. World J.Surg. 1:439-444.

193. Woodward, E.D., Thomas, H.F., McAlhany, J.C. 1971. Comparison of crural repair and nissen fundoplication in the treatment of esophageal hiatal hernia with peptic esophagitis. Ann.Surg. 171:782-789.

194. Skinner, D.B. 1977. Complications of surgery for gastroesophageal reflux. World J.Surg. 1:485-482.

195. Woodward, E.R. 1977. Surgical treatment of gastroesophageal reflux and its complictions. World J.Surg. 1:453-461.

196. Goldstein, R., Butterfield, W. 1973. Modified nissen fundoplication and the "gas-bloat"syndrome as measured by the inability to vomit. Am.J.Surg. 126:89-92.

197. DeMeester, T.R., Johnson, L.F. 1975. Evaluation of the nissen antireflux procedure by esophageal manometry and twenty-four hour pH monitoring. Am.J.Surg. 129:94-100.

198. Siewert, J.R., Blum, A.L. 1979. Post-operative syndrome. The Oesophagus. Clin.Gastroenterol. 8:271-292.

199. Donahue, P.E., Bombeck, C.T. 1977. The modified Nissen fundoplication - reflux prevention without gas-bloat. Chirurgia Gastroenterologica 11:15-27.

200. Vansant, I.H., Baker, I.W. 1976. Complications of vagotomy in the treatment of hiatal hernia. Ann.Surg. 183:629-635.

201. Polk, H.c. 1976. Fundoplication for reflux esophagitis: misadventures with the operation of choice. Ann.Surg. 183:645-652.

202. Hoffmann, T.H., McDaniel, A., Polk, H. 1981. Slippen Nissen's fundoplication: a stitch in time Arch.Surg. 116:1239.

203. Rogers, D.M., Herrington, J.L., Morton, C. 1980. Incidental splenectomy associated with Nissen fundoplication. Ann.Surg. 191:153-156.

204. Herrington, J.L., Meacham, P.W., Hunter, R.M. 1982. Gastric ulceration after fundic wrapping. ann.Surg. 195:574-581.

205. Hill, L.D., Ilves, R., Stevenson, J.K., Pearson, J.M. 1979. Reeoperation for disruption and recurrence after Nissen fundoplication. Arch.Surg. 114:542-548.

206. Lind, J.F., Burns, C.M., MacDougall, J.T. 1965. "Physiological" repair for haitus hernia - manometric study. Arch.Surg. 91:233.

207. Butterfield, W.C. 1971. Current hiatal hernia repairs: similarities, mechanisms, and extended indications - autopsy study. Surgery 69:910.

208. Bowes, K.L., Sarna, S.K. 1975. Effect of fundoplication on the lower esophageal sphincter. Can.J.Surg. 18:328-333.

209. Collis, J.L. 1957. An operation for hiatus herniawith short esophagus. J.Thor.Cardiovasc.Surg. 34:768.

210. Thal, A.T., Hatafuku, T., Kurtyman, R: 1965. New operation for distel esophageal stricture. Arch.Surg. 90:464.

211. Belsey, R. 1965. Reconstruction of the esophagus with left colon. J.Thorac.Cardiovasc.Surg. 49:1.

212. Angelchik, J.P., Cohen, R. 1979. A new surgical procedure for the treatment of gastroesophageal reflux and hiatal hernia. Surg.Gynecol.Obstet. 148:246-248.

213. Starling, J.R., Reichelderfer, M.O., Pellett, J.R., Belzer, F.D. 1982. Treatment of symptomatic gastroesophageal reflux using the Anglechik prosthesis. Ann.Surg. 195:686-691.

214. Belsey, R. 1977. Surgical treatment of hiatus hernia and reflux esophagitis - introduction. World J.Surg. 1:421-423.

215. Nebel, O.T., Fornes, M.F., Castell, D.O. 1976. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Am.J.Dig.Dis. 21:953-6.

216. Weihrauch, T.R. 1981. Esophageal manometry. Methods and clinical practice. Urban & Schwarzenberg. Baltimore-Munich.

217. Babka, J.C., Hager, G.W., Castell, D.O. 1973. The effect of body position on lower esophageal sphincter pressure. Dig.Dis. 18:441-2.

218. Pope, C.E., Meyer, G.W., Castell, D.O. 1981. Is measurement of lower esophageal shincter pressure clinically useful? Dig.Dis.Sci. 26:1025-1031.

219. Hurwitz, A.L., Duranceau, A., Haddad, J.K. 1979. Disorders of esophageal motility. Saunders.

220. Duranceau, A.C., Devroede, G., LaFontaine, E., Jamieson, G.G. 1983. Esophageal motility in asymptomatic volunteers. Surg.Clin.N.Amer. 63:777-786.

221. Marion, L., Sanders, B., Nayfield, S. 1978. Gastric and esophageal dysfunction after ingestion of acid. Gastroenterology 75:502.

222. Rosner, B. 1982. Fundamentals of Biostatistics. Duxbury Press, Boston, Mass.

APPENDIX

Analysis of Probabilities

Theoretical Basis

If X is the number of positive responses in four different tests exhibited by an individual selected at random from the population, P is the event "an individual selected at random from the population has the condition*", and C is the event "an individual selected at random from the population does not have the condition*", it follows by conditional probability that(222):

$$\Pr(X=x \cap C) = \Pr(X=x).\Pr(C|X=x) = \Pr(C).\Pr(X=x|C) \quad (x = 0,1,2,3,4).$$

$$\text{Thus } \Pr(C|X=x) = \frac{\Pr(C).\Pr(X=x|C)}{\Pr(X=x)} \quad \text{(i)}$$

$$\text{Similarly, } \Pr(P|X=x) = \frac{\Pr(P).\Pr(X=x|P)}{\Pr(X=x)} \quad \text{(ii)}$$

$$\text{But } \Pr(P|X=x) = 1 - \Pr(C|X=x),$$

$$\text{and } \Pr(P) = 1 - \Pr(C) \text{ so that (ii) becomes}$$

$$1 - \Pr(C|X=x) = \frac{[1 - \Pr(C)].\Pr(X=x|P)}{\Pr(X=x)} \quad \text{(iii)}$$

Eliminating Pr(X=x) from (i) and (iii) yields

$$\frac{\Pr(C).\Pr(X=x|C)}{\Pr(C|X=x)} = \frac{[1 - \Pr(C)].\Pr(X=x|P)}{1 - \Pr(C|X=x)}$$

* Gastroesophageal reflux disease

and solving for $Pr(C|X=x)$, we obtain

$$Pr(C|X=x) = \frac{Pr(C).Pr(X=x|C)}{Pr(C).Pr(X=x|C) + [1 - Pr(C)].Pr(X=x|P)} \quad (iv)$$

Similarly,

$$Pr(P|X=x) = \frac{Pr(P).Pr(X=x|P)}{Pr(P).Pr(X=x|P) + [1 - Pr(P)].Pr(X=x|C)} \quad (v)$$

Thus, equation (v) permits us to calculate the probability that a randomly selected individual has the condition (given that he exhibits positive responses to x of the four tests) from a knowledge of:

(a) $Pr(P)$ which is the proportion of the whole population having the condition, i.e., the incidence of the condition.

(b) $Pr(X=x|C)$, which is the proportion of individuals not having the condition who exhibit x positive responses to the four tests.

(c) $Pr(X=x|P)$, which is the proportion of individuals having the condition who exhibit x positive responses to the four tests.

Estimation of $Pr(P)$

The actual incidence of gastroesophageal reflux disease is not known. Nebel et al. (1976), in 335 unselected subjects, found an incidence of daily heartburn of 7%, and of heartburn at least monthly of 36%[215]. In the subsequent analysis, an incidence of 5% is assumed, but $Pr(P|X=x)$ will also be computed for a range of incidences from 1% to 40%.

Estimation of $Pr(X=x|\mathbf{C})$

For the control group, a positive response to a test may be viewed as a relatively "rare event". Thus, the Poisson distribution may be considered as a potential model for the distribution of $X^{(223)}$.

For this group, the total number of positive responses was 14|41. Thus, the mean no. of positive responses was 0,3415.

The Poisson model would estimate $Pr(X=x|\mathbf{C})$ by

$$q(x) = \frac{0.3415^x \cdot e^{-0.3415}}{x!}, \quad (x=0,1,2,3,4)$$

and the corresponding predicted frequency by

$$Q(x) = 41.q(x)$$

Table 26 gives the estimated values $q(x)$ of the probabilities $Pr(X=x|\mathbf{C})$ and compares the observed frequencies $A(x)$ with those predicted by the Poisson model $Q(x)$. Comparing the observed and predicted frequencies, we see that the fit of the Poisson model is remarkably good. Indeed, if the predicted frequencies are rounded to the nearest integer values, the fit is exact. Thus, we may proceed with assurance in estimating $Pr(X=x|\mathbf{C})$ by the values of $q(x)$ given in Table 26.

Estimation of $Pr(X=x|\mathbf{P})$

The probabilities $Pr(X=x|\mathbf{P})$ are estimated by $p(x)$ obtained by reversing the Poisson model. A non-positive test in the patient group is thus regarded as a relatively "rare event". If Y is the number of non-positive tests, and $Y = 4 - X$, the Poisson model is fitted to the frequency distribution of Y and $Pr(X=x|\mathbf{P})$ is calculated by

$$Pr(X=x|\mathbf{P}) = Pr(Y=4-x|\mathbf{P}).$$

The total no. of non-positive tests in the patient group was 71|68. Thus the mean number of non-positive tests was 1.0441.

The Poisson model estimates $Pr(Y=4-x|\mathbf{P})$ and thus $Pr(X=x|\mathbf{P})$ by

$$p(x) = \frac{1.0441^{(4-x)} \cdot e^{-1.0441}}{(4-x)!}$$

Letting B(x) and R(x) be respectively the observed and predicted frequencies for the patient group, Table 27 gives the estimated values p(x) of the probabilities $Pr(X=x|\mathbf{P})$ and compares the observed frequencies B(x) with those predicted by the Poisson model R(x). The fit of the Poisson model, although not quite as good as for the control group, is still very acceptable by the usual Chi-square test of goodness of fit.

Estimation of $Pr(\mathbf{P}|X=x)$

Using equation (v), the probabilities of having the disease are calculated for each of the given number of test results, with $Pr(X=x|\mathbf{P})$ estimated by p(x), $Pr(X=x|\mathbf{C})$ by g(x), and a range of values for Pr(P) from 0.01 to 0.40. Table 28 gives the $Pr(\mathbf{P}|X=x)$ values for an incidence level of 5%, i.e., Pr(P) = 0.05, and Table 17 gives the values of $Pr(\mathbf{P}|X=x)$ values for Pr(P) values from 0.01 to 0.40.

Table 26

Values of q(x) and comparison of observed frequences A(x) with predicted frequencies Q(x) for the control subjects, where x is the number of positive test responses.

x	q(x)	A(x)	Q(x)
0	0.7107	29	29.14
1	0.2427	10	9.95
2	0.0414	2	1.70
3	0.0047	0	0.19
4	0.0004	0	0.02

Table 27

Values of p(x) and comparison of observed frequencies B(x) with predicted frequences R(x) for the patient group, where x is the number of positive test responses.

x	p(x)	B(x)	R(x)
0	0.0174	2	1.18
1	0.0668	3	4.54
2	0.1919	15	13.04
3	0.3675	24	24.99
4	0.3520	24	23.93

Table 28

Estimated probabilities of having gastroesophageal reflux disease for a given no. of positive test results at the 5% incidence level.

No. of Positive Tests	Estimated probability of having GE reflux	
0	.0035	(0%)
1	.0265	(3%)
2	.2419	(24%)
3	.7894	(79%)
4	.9671	(97%)